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CONTENTS

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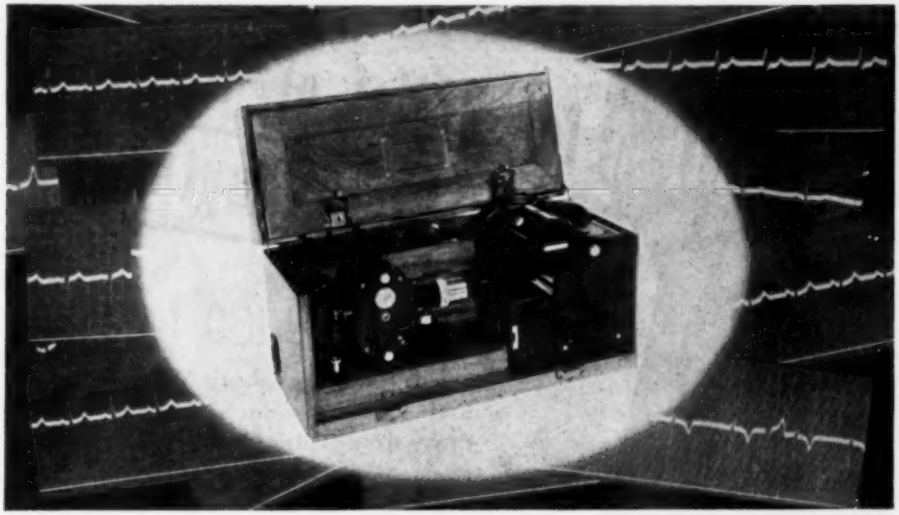

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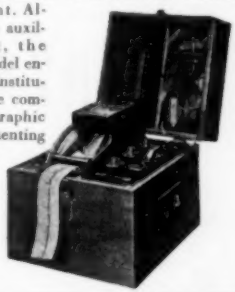

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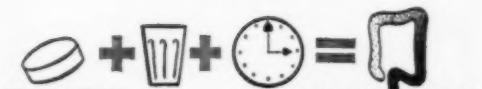
1. "A Method of Improving Function of the Bowel": J. Arnold Bargen, M.D., Division of Medicine, Mayo Clinic, Rochester, Minnesota, in Gastroenterology, 13:275 (Oct.) 1949.



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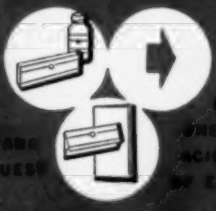

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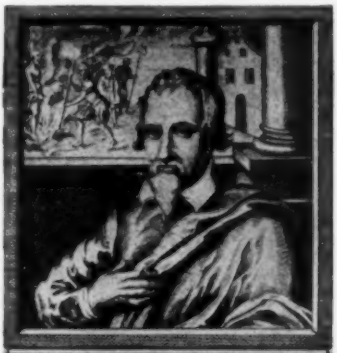

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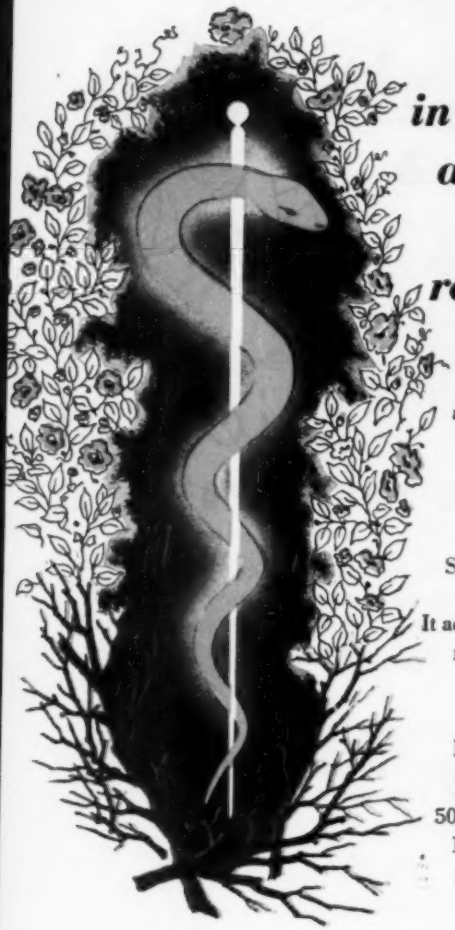

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Smadel, J. E.: J.A.M.A. *141*:315, 1950 (discussion)

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Hewitt, W. L., and Williams, B., Jr.: New England J. Med. *242*:119, 1950

"**NO toxic reactions** or signs of intolerance were observed."

Payne, E. H.; Knaudt, J. A., and Palacios, S.: J. Trop. Med. & Hyg. *51*:88, 1948

"**NO symptoms or signs of toxic effects** attributable to the drug were observed."

Ley, H. L., Jr.; Smadel, J. E., and Crocker, T.: Proc. Soc. Exper. Biol. & Med. *68*:9, 1948

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ANNALS OF
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VOLUME 32 MAY, 1950 NUMBER 5

RETROGRADE ARTERIOGRAPHY IN THE DIAGNOSIS OF CARDIOVASCULAR LESIONS. II. COARCTATION OF THE AORTA *

By NORMAN E. FREEMAN, M.D., EARL R. MILLER, M.D., H. BRODIE STEPHENS, M.D., and MARY B. OLNEY, M.D.,
San Francisco, California

IN a previous communication [1] the usefulness of retrograde arteriography in the diagnosis of aneurysms and peripheral vascular lesions was discussed. The present paper is concerned with the visualization of the thoracic aorta and its branches by means of radiopaque material injected into the common carotid artery in a retrograde fashion. This technic has been of use in the diagnosis and localization of coarctation of the aorta.

At the time that Farinas [2] demonstrated his studies on retrograde arteriography for visualization of the abdominal aorta at the radiological meetings in Chicago in 1944, it occurred to one of us (E. R. M.) that a similar procedure might be of use in visualizing abnormalities of the aorta and its great branches. The diagnosis of coarctation of the aorta can be inferred from the notching of the ribs seen at the time of routine radiologic examination of the chest. Although it has been possible to visualize the region of the coarctation by means of angiocardiography,[3, 4] we have not been satisfied with the demonstration of the precise location and extent of the narrowing of the aorta by this technic. A more precise method of visualization was therefore desirable. Retrograde carotid arteriography has been employed by us in 15 patients with a clinical diagnosis of coarctation of the aorta. The examination was successful in 13 of these patients, and there have been no serious complications. It has been possible to demonstrate the location, type, and degree of coarctation in a majority of these patients. In four cases the examination saved the patient from an unnecessary thoracotomy.

* Received for publication March 5, 1949.
From the Divisions of Surgery, Radiology, and Pediatrics, University of California School of Medicine, San Francisco 22, California.

Technic

Under local or general anesthesia the left common carotid artery is exposed above the sternoclavicular joint, dissected free for a distance of 5 centimeters, and surrounded by a segment of rubber tubing (figure 1). The patient is then taken to the x-ray department, and after a preliminary film has been made a large needle is inserted directly into the carotid artery in a proximal direction. The needle is attached by a segment of rubber tubing to a syringe containing the contrast medium. Seventy per cent diodrast has been found to be a satisfactory material. The dose is approximately 1 c.c. per kilogram of body weight up to a maximum of 50 c.c. In children an

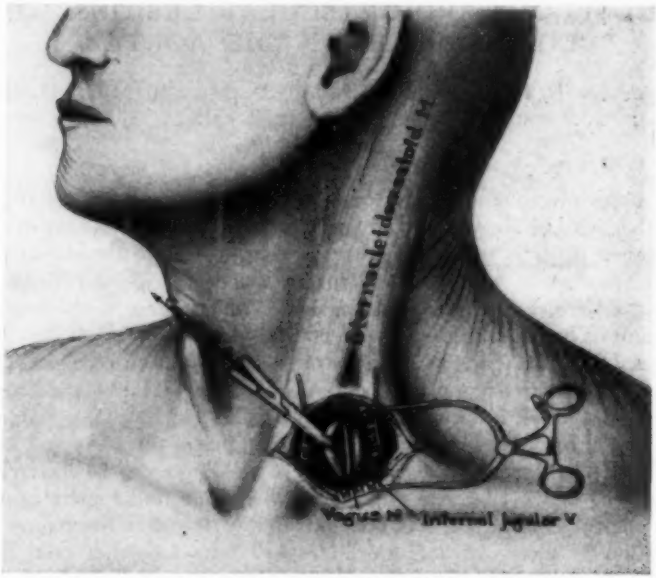

Fig. 1. Surgical exposure of left common carotid artery for retrograde arteriography.

18-gauge needle is used, but in adults a No. 16 is preferable. At a given signal the material is injected as rapidly as possible and serial x-ray exposures are taken. Traction on the tubing surrounding the artery occludes it distally and prevents the flow of diodrast into the head. After completion of the exposures, special care is taken to aspirate the diodrast remaining in the carotid artery *before* release of the rubber tubing, in order to prevent this irritating material from reaching the cerebral circulation. Upon withdrawal of the needle the puncture site is controlled by arterial clamps placed above and below the opening, the patient is returned to surgery, and after the wound has been flushed out thoroughly, the opening

in the artery is closed with a single figure-of-eight stitch of No. 00000 Deknatel. Except for one instance in which there was extravasation of blood into the tissues leading to the formation of a hematoma, there has been no further bleeding from the carotid artery.

On three occasions there was extravasation of dye, probably due to dislodgement of the needle at the time of the forceful injection. In order to prevent displacement of the needle a segment of rubber tubing has subsequently been used between it and the syringe. The needle is held with a hemostat by an assistant.

The following roentgenographic technic has been used. The patient is placed supine on a horizontal cassette tunnel with the long axis of the tunnel and the long axis of the x-ray table on which it is placed running in the same direction. The tunnel is open on both of its longer sides and is large enough to permit the easy passage of a 14 by 17-inch film cassette through it. A stationary grid is fastened to the top of the tunnel. To check the position of the patient and the technic, a preliminary film is taken, using a target film distance of 40 inches, 400 milliamperes, an exposure of one-tenth to one-fifth of a second, and a voltage adjustment to show the thoracic spine detail. It is imperative that the first film of the series be taken immediately on completion of the injection and the remaining two to three films be exposed as rapidly as the cassettes can be changed by hand (about every two seconds).

Results

In the first case that was studied, retrograde carotid arteriography demonstrated a normal thoracic aorta.

Case 1. This patient was a 32 year old married woman who, at the age of 13, during routine physical examination by her school physician, was found to have hypertension. She had had a low exercise tolerance and some palpitation. At the time of hospital admission the blood pressure in the upper extremities was found to be 200/140. No femoral pulsations were felt. The blood pressure in the left leg was 130/120. The blood pressure could not be obtained in the right leg. With immersion of one hand in ice water the blood pressure rose from 190/134 to 208/160, and with sodium amytal the blood pressure fell to 138/98. Palpation for collateral vessels showed that the subclavian and axillary arteries were of normal size, and no collateral vessels could be felt about the scapulae or upper portion of the thorax. On close examination it was found that she had increased pulsations of the intercostal blood vessels in the lower thorax and it was possible to feel pulsation of arteries about the umbilicus and the iliac .ts. There was no murmur over the precordium, but auscultation over the lower thorax and abdomen revealed a soft systolic murmur which was best heard in the epigastrium midway between the xiphoid and the umbilicus. Reëxamination of the x-ray films disclosed some notching of the lower thoracic ribs.

With the possibility in mind that the patient might have coarctation of the aorta below the diaphragm similar to the cases described by Steele,[5] retrograde arteriography was performed. Twenty c.c. of 25 per cent thorotrast were injected through an 18-gauge needle. It was possible to visualize the upper thoracic aorta which was of normal size below the subclavian artery (figure 2). Insufficient dye was injected to define the lower thoracic aorta or abdominal aorta.

Comment: On the basis of this study, exploratory thoracotomy was considered to be inadvisable and the patient was discharged on a medical regimen.

The second patient with definite clinical signs of coarctation of the aorta was shown by retrograde arteriography to have a narrowing of the lower thoracic and abdominal aorta.

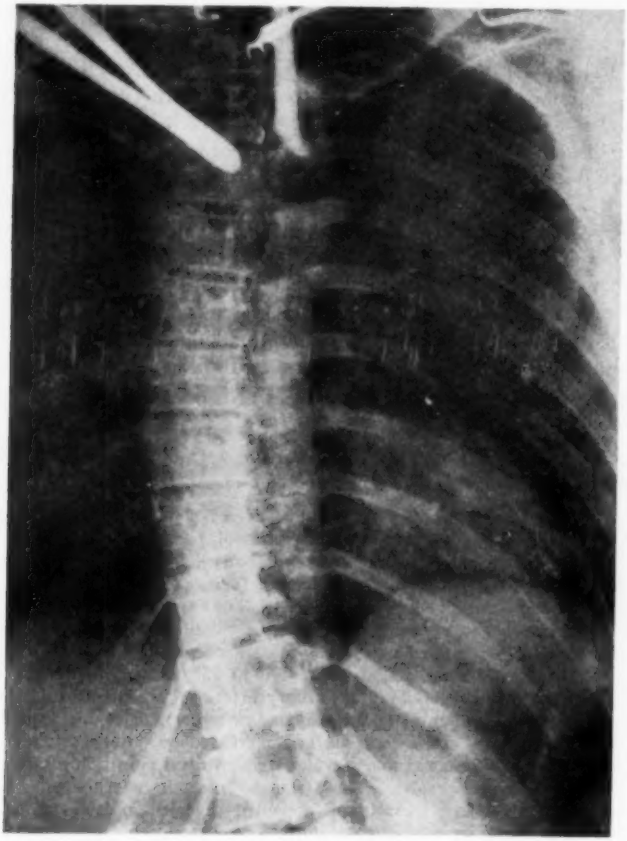

FIG. 2. (*Case 1.*) The upper portion of the thoracic aorta is seen to be of normal size. The exact location of the stenosis is not demonstrated.

Case 2. This patient was a 14 year old girl with multiple congenital defects, including marked scoliosis and kyphosis of the thoracic spine. She had been short of breath for some years, had never been cyanotic and had never shown signs of heart failure. At the age of nine she had suffered a cerebrovascular accident with a residual left hemiplegia. On physical examination at the time of admission there was a loud systolic murmur over the precordium, best heard in the third left interspace

and transmitted along the spine and ribs into the abdomen. The blood pressure in the right arm was 225/125 and in the legs the systolic pressure was 130. The femoral pulses were not palpable, and no pulsation of the abdominal aorta could be felt. The urine and blood examinations were essentially normal.

Retrograde carotid arteriography was performed with the injection of 20 c.c. of 70 per cent diodrast through the left common carotid artery. At the first injection there was extravasation of the dye, and a second injection was necessary. This examination (figure 3) revealed extensive collateral circulation, particularly in the

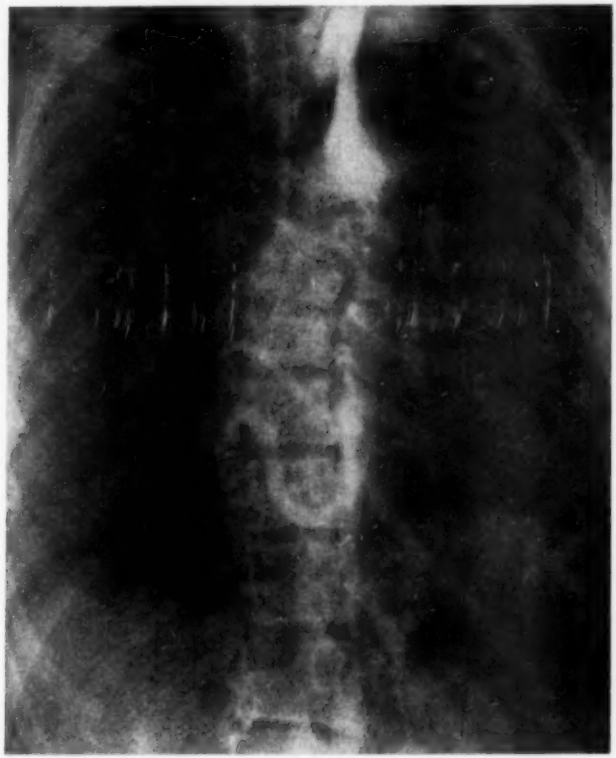

FIG. 3. (*Case 2.*) Stenosis of the lower portion (T11–L1) of the thoracic aorta.

lower thoracic region, with narrowing of the aorta in the region of T11 to L1. Below this point the aorta assumed a more normal diameter. On the basis of these studies a restorative procedure was deemed technically impossible.

Comment: This patient was spared an unnecessary exploratory thoracotomy by the use of retrograde arteriography.

In the next case it was possible to exclude the diagnosis of coarctation of the aorta.

Case 3. This patient was an underdeveloped 13 month old female in whom a systolic murmur over the precordium was discovered on routine physical examination. The heart was enlarged and the electrocardiogram showed changes consistent with left ventricular hypertrophy. Both lower extremities were cold, but the blood pressure was approximately equal in the arms (110/78) and the legs (110/60). The plain films of the heart suggested pulmonary hypertension, so that the possibility of patent ductus arteriosus was considered. Retrograde arteriography was performed with the injection of 10 c.c. of diodrast through an 18-gauge needle into the left common carotid artery. The aorta and the vessels appeared to be normal and the pulmonary vessels were not visualized. There was some extravasation of dye at the time of this examination and, because the results were somewhat inconclusive, a second injection was made. Complete visualization of the aorta and all of its branches was obtained, and the possibility that the cardiac lesion was due to some abnormality of the aorta or one of its branches was definitely excluded.

Retrograde carotid arteriography for visualization of the thoracic aorta is also of use in evaluation of the degree of constriction of the aorta, as shown in the following case.

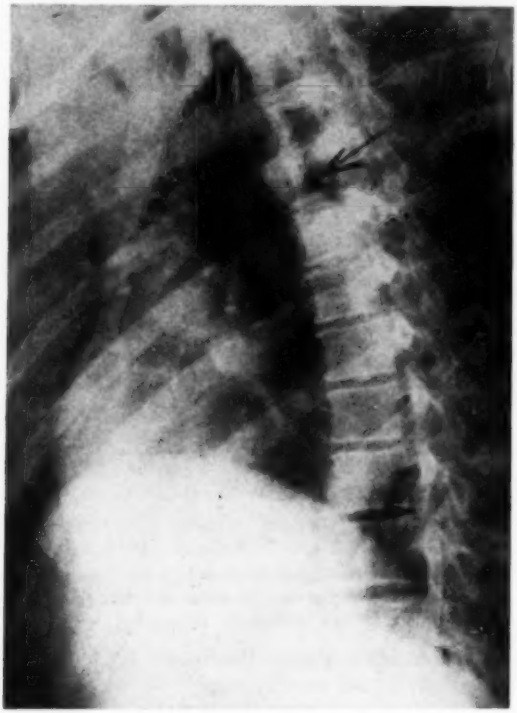

FIG. 4. (*Case 4.*) Moderate stenosis of aorta without extensive collateral circulation.

Case 4. This patient was a 30 year old married woman who was admitted to the cardiovascular clinic with the chief complaint of attacks of high blood pressure for 15 months, associated with weakness, palpitation, and convulsions. Hypertension was first noted at the age of 15. There had been no cyanosis. She had been under observation for many months because of a variety of functional disturbances. The electrocardiogram was found to be normal. Auscultation of the chest revealed a harsh systolic murmur of maximal intensity in the second left interspace, transmitted through into the back. The abdominal aorta was not felt and the femoral pulsations were reduced. Blood pressure in the right arm was 150/80 and the systolic pressure in the right leg was 110. The diagnosis upon admission was coarctation of the aorta with a severe anxiety state.

Retrograde carotid arteriography was performed with the injection of 50 c.c. of 35 per cent diodrast in 4.5 seconds, through a 15-gauge needle. Only the first film showed dye in the aorta (figure 4). There was definite narrowing of the thoracic aorta just below the arch, with poststenotic dilatation. Measurements of the aorta were as follows: Above the region of coarctation, 21 mm.; at the level of the narrowing, 10 mm.; below, 30 mm., in diameter. The collateral circulation was not extensive. The patient was discharged on a medical regimen.

Comment: It was possible in this patient to demonstrate the coarctation and to determine that it was not sufficiently severe to warrant operative intervention.

In Case 5 and Case 6, examination by retrograde carotid arteriography was unsatisfactory. Both of these patients were large, heavy-set adults, and only 30 c.c. of 70 per cent diodrast were injected through 16-gauge needles. Although coarctation of the aorta was inferred from the presence of multiple collateral blood vessels, the actual zone of narrowing was not demonstrated. In both of these patients it was felt that the technical difficulties of thoracotomy and aortectomy would be too great to warrant operation.

In the remaining nine cases (table 1) the coarctation of the aorta was adequately demonstrated, and in all of these patients the presence and degree of the lesion were confirmed at operation.

Case 7. This patient was a 34 year old man who had classic signs of coarctation of the aorta and moderate progressive cardiac failure. There were marked abnormal pulsations of collateral vessels, and the blood pressure in the arms was 200/70, in the legs 110/70. He was known to have had hypertension for at least nine years, and for 10 months prior to his admission he had had dyspnea on exertion, with severe stabbing pains over the precordium. There had been marked weight loss during the preceding two months, with paroxysmal nocturnal dyspnea. Electrocardiograms showed left ventricular hypertrophy with a suggestion of an anterior septal myocardial infarction. Renal function was normal. Retrograde arteriography was performed with the injection of 20 c.c. of 25 per cent thorotrast through the left common carotid artery. The thoracic aorta was not demonstrated, but great dilatation of the left subclavian artery was shown. At the time of operation marked degenerative changes in the aorta proximal to the zone of narrowing were observed. The stenotic region was resected and an end-to-end anastomosis of the aorta was made. Post-operatively, recovery was uneventful. The blood pressure in the arms came down to 150/70; in the legs it rose to 170/110. On the eleventh day the patient had sudden pain over the precordium, collapsed and died. Postmortem examination revealed a rupture of the aorta just above the suture line.

TABLE I

Case No.	Sex	Age	Date Study	B. P. Pre. Op.		B. P. Post Op.		Contrast Material	Anesthesia	Needle Gauge	Complications	Comment
				Arm	Leg	Arm	Leg					
1	F	32	11/1/46	190/134	130/120	—	—	20 c.c. Thorotrast	Endotrach.	18	Hematoma	Examination excluded coarctation of thoracic aorta
2	F	14	12/8/47	225/125	130/?	—	—	20 c.c. 70% D	Endotrach.	—	Extravasation of dye	Extensive narrowing of aorta T11–L1
3	F	1	11/5/47	110/78	110/60	—	—	10 c.c. 70% D	Ether	18	Extravasation of dye	Examination excluded coarctation of thoracic aorta
4	F	30	7/28/47	150/80	110/?	—	—	50 c.c. 35% D	Local	15	—	Coarctation not severe
5	M	19	10/20/47 10/29/47	222/130	?	—	—	30 c.c. 70% D 30 c.c. 70% D*	Cerv. Block Ether	16 16	Extravasation of dye	Probable coarctation but exact level not established
6	M	35	10/22/47	210/110	?	—	—	30 c.c. 70% D	Endotrach.	16	—	Probable coarctation but exact level not established
7	M	34	1/2/47	200/70	110/70	150/170	170/110	20 c.c. Thorotrast	Local	18	—	Coarctation confirmed at operation
8	M	4½	5/12/47	125/75	106/90	126/68	144/96	25 c.c. 35% D	Endotrach.	18	—	Coarctation confirmed at operation
9	M	16	10/15/47	180/105	?	Rt. 180/90 Lt. 0	110/?	30 c.c. 70% D	Local	—	—	Coarctation confirmed at operation
10	M	1	12/4/47	132/85	85/70	—	—	9 c.c. 70% D	Ether	—	—	Coarctation confirmed at operation
11	M	5	1/15/48 3/9/48	Rt. 0 Lt. 158/80	70/?	Rt. 110/90 Lt. 0	120/100	15 c.c. 70% D 20 c.c. 70% D	Endotrach. Ether	—	Extravasation of dye	Coarctation confirmed at operation
12	M	16	3/26/48	160/110	90/80	156/86	146/96	50 c.c. 70% D	Local	16	—	Coarctation confirmed at operation
13	M	19	4/2/48	192/124	120/60	160/100	150/100	37 c.c. 70% D	Local	18	—	Coarctation confirmed at operation
14	M	15	5/5/48	180/100	118/100	142/80	155/94	50 c.c. 70% D	Local	16	—	Coarctation confirmed at operation
15	M	24	9/17/48	190/100	90/70	138/78	125/90	50 c.c. 70% D	Local	16	—	Complete stenosis found at operation

* Right carotid used.

Comment: This was the second patient in whom visualization of the coarctation was attempted but too little of the contrast medium was injected for a satisfactory delineation of the lesion. In retrospect, in view of the extent of the degenerative changes in the aorta, it would have been better in this case to have performed an anastomosis between the left subclavian artery and the aorta.

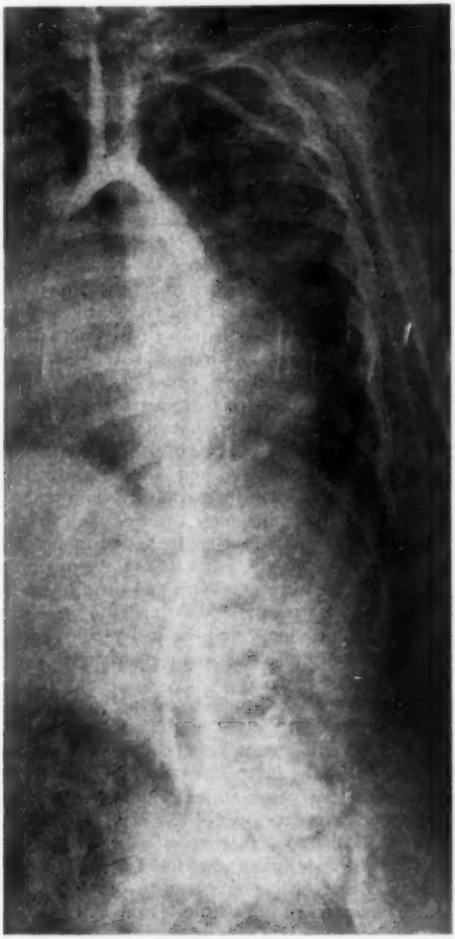

FIG. 5. (*Case 8.*) Coarctation of the aorta in a boy aged four and one-half years.

Case 8. This patient was a four and one-half year old boy who was admitted with the chief complaint of marked weakness of five months' duration. He was sup-

posedly in normal health until the age of three, when it was noted that he had a precordial bulge. Six months before admission he manifested extreme weakness after play, and his legs buckled under him. He was referred to the pediatrician with the diagnosis of rheumatic fever. At the time of admission the blood pressure in the arms was 125/75 and in the legs, 106/90. There was a blowing systolic murmur over the precordium. The heart was markedly enlarged and femoral pulsations were not palpable.

Angiocardiography by the intravenous route revealed a small aorta which was considered to indicate a general hypoplasia. Retrograde carotid arteriography with the injection of 25 c.c. of 35 per cent diodrast demonstrated the coarctation of the aorta just below the arch (figure 5). A resection of the region of coarctation was accomplished with end-to-end anastomosis of the thoracic aorta. After operation the blood pressure in the right arm was 126/68 and in the right leg, 144/96. There has been an uneventful recovery, and the child is now normally active, with no residual symptoms.

Case 9. This patient was a 16 year old boy admitted to the University of California Hospital with the diagnosis of coarctation of the aorta. Hypertension had been discovered during routine physical examination four years before admission. At that time it was noted that the femoral pulsations were absent. Seven years before admission, he had developed symptoms of weakness in the legs following exercise and also complained of throbbing frontal headaches. On admission to the hospital the blood pressure was 180/105 in the right arm and was unobtainable in the legs. The femoral pulses were barely palpable on either side. The heart was not enlarged by x-ray examination, and the circulation time was normal. The kidney function was normal. The red blood cell count was six million per cubic mm. Electrocardiograms showed left ventricular hypertrophy. There was marked development of collateral blood vessels in the thoracic wall. Retrograde arteriography was performed with the injection of 30 c.c. of 70 per cent diodrast. Serial films revealed hypoplasia of the transverse arch and definite coarctation below the origin of the subclavian artery with dilatation of the aorta below the region of narrowing. There was also some dye in the pulmonary arteries, indicating the presence of a patent ductus arteriosus which was subsequently found at operation. The left subclavian artery was anastomosed to the aorta below the region of stenosis. After operation the pulses in the legs were excellent, and on the eighth postoperative day the blood pressure in the right arm was 180/90 and the systolic pressure in the leg was 110. A left hemothorax developed and the patient died four weeks after operation. Failure of healing at the suture line was demonstrated at postmortem examination.

Case 10. This patient was a 13.5 month old boy admitted with cardiac decompensation. A precordial bulge and a heart murmur had been noted soon after birth. The patient gradually developed signs of heart failure with generalized anasarca and enlargement of the liver. On physical examination there was found to be a systolic murmur in the third left interspace, transmitted to the upper portion of the back. The blood pressure in the upper extremities was 132/85. The femoral pulses were weak. With digitalis and oxygen therapy, there was marked improvement. Retrograde arteriography was performed under ether anesthesia, with the injection of 9 c.c. of 70 per cent diodrast. Marked narrowing of the aorta just below the origin of the left subclavian artery was demonstrated. The stenotic area was resected and an end-to-end anastomosis of the thoracic aorta was made. The stenosis of the aorta in this case was extreme, the opening measuring only 1.5 mm. in diameter. The child died at the conclusion of the operation, just as he was recovering from the anesthetic.

Case 11. This patient was a 5 year old boy. On physical examination a

machinery type of murmur was heard over the entire precordium, transmitted into the back. The pulse was absent in the right upper extremity. Blood pressure in the left arm was 135/70 and the systolic pressure in both legs was 70. The femoral pulses were faint on both sides. Retrograde carotid arteriography on the left side was performed, with the injection of 15 c.c. of 70 per cent diodrast. There was some extravasation of dye. The distal portion of the aorta and the branches filled well, but the presence of the dye in the periaortic tissues obscured the site of the stenosis. At this time the diagnosis of coarctation of the aorta was still in doubt and the child was discharged. He was readmitted six weeks later when arteriography was repeated, the injection again being made into the left common carotid artery. At this time there was considerable difficulty in exposing the artery because of the dense scar tissue from the previous extravasation of diodrast. However, 20 c.c. of 70 per cent diodrast were injected and the examination showed a definite coarctation of the aorta at the beginning of the descending arch. The left subclavian artery was anastomosed to the aorta below the zone of coarctation. A large anomalous vessel found leading into the area of the coarctation was carefully preserved at the time of operation. Immediately after operation the blood pressure in the legs was 150/110 and in the right arm, where there had been no pulse palpable before operation, the blood pressure was 120/100. This child recovered from operation and the final blood pressure in the right arm was 100/90 and in both legs, 110/82.

Case 12. This 16 year old boy was known to have had a heart murmur since the age of five. He was normally active in school sports, but had noted for the past four or five years that his legs became weak with strenuous exercise. Two years before admission his blood pressure was found to be 160/110 in the arms, 90/80 in the legs. His heart was enlarged and the electrocardiographic record suggested myocardial disease. On physical examination there was a loud systolic murmur heard over the apex and transmitted to the left thoracic region posteriorly. There were marked pulsations of the axillary and intercostal arteries and of the collateral arteries about the chest wall and scapulae. Femoral pulses were barely palpable on both sides. Retrograde arteriography was performed, with the injection of 50 c.c. of 70 per cent diodrast through a No. 16 needle. The first film showed the proximal aorta and the collateral vessels, but the aorta below the zone of constriction was not clearly visualized. The second film showed filling of the aorta and the collateral vessels in the lower thorax, indicating that relatively little blood was traversing the region of stenosis. Subsequently the stenotic area was resected with end-to-end anastomosis of the aorta. The following day the blood pressure in the right arm was 152/100, in the right leg, 120/90. The patient made an excellent recovery and was discharged on the tenth postoperative day. Two months after operation, the blood pressure in the arms was 156/86 and in the legs 146/96.

Case 13. This patient was a 19 year old male. Four years before admission he had noted headaches with dizziness, and his systolic blood pressure was found to be 190. Six months prior to entry the patient had noticed easy fatigability, occasional headaches, with faintness and blurred vision and a loss of 20 pounds in weight. There was some dyspnea on exertion, and there were episodes of palpitation. Examination showed marked pulsation of collateral vessels over the thorax, and diminished femoral pulsations. X-ray examination showed scalloping of the ribs and moderate cardiac enlargement. At the time of admission the blood pressure in the upper extremity was found to be 155/85 and in the lower extremity, 120/60. The renal function was normal. Electrocardiogram showed left ventricular hypertrophy. Retrograde carotid arteriography was performed, with the injection of 37 c.c. of 70 per cent diodrast through an 18-gauge needle. Although visualization of the aorta was not entirely satisfactory, a coarctation was demonstrated just distal to the left subclavian artery. The patient was operated upon and the end of the subclavian

artery anastomosed to the end of the aorta below the region of stenosis. Satisfactory recovery took place, although the blood pressure in the upper extremity did not come down to a normal level. On examination five months postoperatively, the blood pressure in the right arm was found to be 160/100 and in the right leg, 150/100.

Case 14. This patient was a 15 year old schoolboy. On routine physical examination, a blood pressure of 180/100 was found in his upper extremities. He had noted increasing weakness and fatigability, especially of the lower extremities, but had participated actively in school athletics. Upon admission the blood pressure in the right arm was found to be 180/100, in the left leg, 118/100. The urine was not

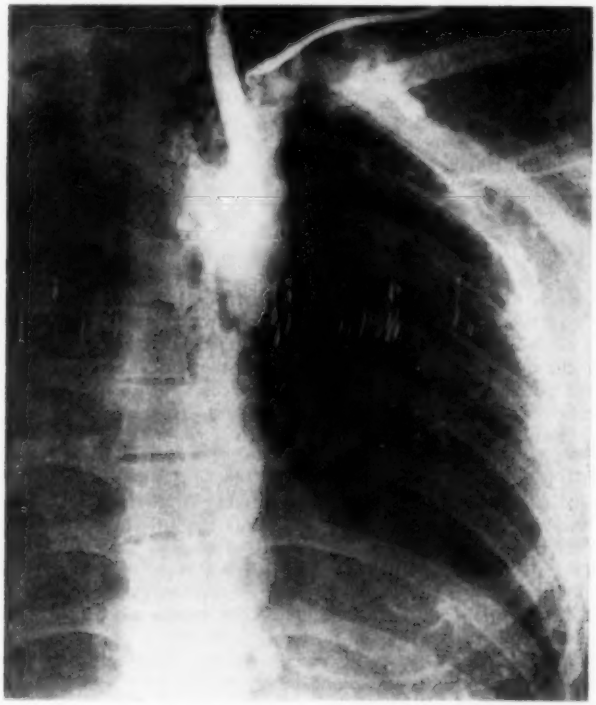

FIG. 6A. (*Case 15.*) Film taken at the conclusion of the injection. The aorta above the stenotic region is well filled.

abnormal, and the electrocardiogram was within normal limits. Retrograde carotid arteriography was performed, with the injection of 50 c.c. of 70 per cent diodrast through a 16-gauge needle. Excellent demonstration of the coarctation was obtained, but the collateral circulation was not as extensive as had been observed in other cases. He was readmitted to the hospital two months later, and at operation the stenotic area was excised and the aorta repaired by an end-to-end anastomosis. The patient did very well after operation; was out of bed on the fourth day and discharged on the eighth day. Two days after operation the blood pressure in the upper extremity was 142/80 and 155/94 in the lower extremity. Subsequently the pressures have come down to normal.

Case 15. The patient was a 24 year old man who was found to have a heart murmur at the age of 14. At the age of 19 he was operated upon for abdominal pain, and greatly increased collateral circulation was noted in the abdominal wall. For three years before admission, he had been aware of increasing dyspnea and fatigability. The blood pressure in the right arm was found to be 192/102, in the right leg, 110/80. X-ray examination revealed notching of the ribs and enlargement of the heart. The

FIG. 6B. (*Case 15.*) Film taken two to three seconds after figure 6A. The aorta below the zone of coarctation is now well filled.

electrocardiogram showed an abnormal record characteristic of right bundle branch block. He was admitted to the hospital, where the blood pressure was found to be 180/105 in the upper extremities, 145/100 in the lower extremities. There were marked pulsations of the collateral blood vessels about the upper thorax and back. Urine and blood examinations were normal. Arteriography, with the injection of 50 c.c. of 70 per cent diodrast into the left common carotid artery through a 16-gauge needle, showed a marked coarctation of the aorta below the left subclavian artery, and

extensive collateral circulation in the chest wall. It is interesting to note (figure 6) that the aorta below the constriction did not fill until the second film was taken, indicating that very little blood was passing the area of stenosis. At operation the aorta was found to be completely occluded. The stenotic region was resected and the aorta repaired with an end-to-end anastomosis. Postoperatively the pulses in the lower extremities were full. One week after operation the blood pressure in the right leg was 180/120 and in the right arm, 174/106.

Discussion

Coarctation of the aorta is a condition which is now amenable to surgical correction. If untreated, most of the patients will die at a relatively early age. In 196 cases of the adult type collected by Blackford,[6] the coarctation was fatal in 147. Death occurred from gradual heart failure in 68 of these patients, from rupture of the aorta in 38, and from cerebral hemorrhage in 25. Of the 200 cases in Abbott's series, almost three-fourths of the patients died before the fortieth year.

The diagnosis of coarctation of the aorta is not difficult and should be suspected in all children and young adults with hypertension. Diminution or absence of the femoral pulses will frequently support this diagnosis, and search should then be made for evidence of increased collateral circulation about the upper thorax. Roentgen examination of the thorax is of value but is not infallible, since notching of the ribs, first described by Railsbach and Dock,[7] is not invariably seen. In children, before the development of extensive collateral circulation, it is rare to find indentation of the ribs. Other features in the x-ray study, to which Gladnikoff [8] has called attention, are the dilated left subclavian artery and the absence of the aortic knob. These findings, when present, suggest the diagnosis, but do not give proof of the presence of coarctation of the aorta. Demonstration of the lesion by angiocardiography, with the use of diodrast intravenously, was first reported by Robb and Steinberg.[3] Their technic was subsequently used in two cases by Grishman, Steinberg, and Sussman.[4] There was an abrupt disappearance of the aortic shadow just below the arch, and dilated collateral channels were visualized. One of us (E. R. M.) had studied by intravenous angiocardiography 10 patients with the clinical diagnosis of coarctation of the aorta, but in no case was the demonstration of the stenotic segment entirely satisfactory. The dilated collaterals could be seen and there was an absence of filling of the descending aorta, but the concentration of dye was insufficient to outline clearly the stenotic region. It was therefore felt that introduction of the radiopaque material into the aorta directly above the zone of narrowing would give more satisfactory results. Because the left common carotid artery arises from the aortic arch proximal to the usual location of the constriction, this vessel was chosen for retrograde injection.

By this procedure it is possible to show not only the exact location of the coarctation, but also the degree and the extent of the stenosis. Unnecessary thoracotomy was avoided in four of our patients.

In Case 1 the thoracic aorta below the arch was of normal size, whereas in Case 2 the narrowed segment was found to extend from the eleventh thoracic to first lumbar spine. In Case 3 the possibility of coarctation of the aorta was excluded by visualization of this vessel, and in Case 4 the degree of stenosis was found to be insufficient to warrant operation. In two patients the examination was technically unsatisfactory, although extensive development of collateral circulation indicated that there was coarctation of the aorta. In the remaining nine cases the demonstration was satisfactory and the diagnosis in each case was confirmed at operation.

The rapidity with which the aorta below the stenotic region filled with the dye depended upon the degree of obstruction. In Case 15, in which the obliteration was complete, the first film, taken at completion of the injection, outlined the proximal aorta, subclavian artery, and some of the upper collaterals. The aorta distal to the stenosis was visualized only faintly. On the second exposure, taken two to three seconds later, the lower segment of aorta filled more densely and the lower collaterals were demonstrated. By comparison, in Case 14 the lower segment of the aorta was readily demonstrated on the first exposure. The collateral circulation was not as extensive. At operation the lumen of the aorta measured 2 to 3 mm. in diameter at the point of greatest narrowing.

Summary

Retrograde arteriography has been used in 15 patients in whom the diagnosis of coarctation of the aorta had been made on clinical findings. The injection has been made into the left common carotid artery in all cases. Seventy per cent diodrast has been found to give the most satisfactory results. The examination was satisfactory in 13 of the 15 cases. In one patient a hematoma developed in the wound; there have been no other complications. In nine of the patients the exact location, degree, and extent of the stenosis were visualized, and these findings were confirmed at operation.

BIBLIOGRAPHY

1. Freeman, N. E., and Miller, E. R.: Retrograde arteriography in the diagnosis of cardiovascular lesions. I. Visualization of aneurysms and peripheral arteries, Ann. Int. Med. **30**: 330–342, 1949.
2. Farinas, P. L.: Retrograde abdominal aortography, Am. J. Roentgenol. **55**: 448, 1946.
3. Robb, G. P., and Steinberg, I.: Visualization of the chambers of the heart, the pulmonary circulation and the great blood vessels in man: summary of method and results, J. A. M. A. **114**: 474, 1940.
4. Grishman, A., Steinberg, M. F., and Sussman, M. L.: Contrast roentgen visualization of coarctation of the aorta, Am. Heart J. **21**: 305, 1941.
5. Steele, J. M.: Evidence for general distribution of peripheral resistance in coarctation of the aorta: report of three cases, J. Clin. Investigation **20**: 473, 1941.
6. Blackford, L. M.: Right aortic arch, Am. J. Dis. Child. **44**: 823, 1932.
7. Railsbach, O. C., and Dock, W.: Erosion of the ribs due to stenosis of the isthmus (coarctation) of the aorta, Radiology **12**: 58, 1929.
8. Gladnikoff, H.: The roentgenological picture of the coarctation of the aorta and its anatomical basis, Acta Radiol. (Stock.) **27**: 8, 1946.

THE TWO-STEP EXERCISE ELECTROCARDIOGRAM: A TEST FOR CORONARY INSUFFICIENCY *

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Diagnosis of heart disease is often complicated by the fact that objective evidence of organic disease cannot be obtained. In many cases of coronary disease with angina pectoris, physical examination, roentgenographic representation of the size of the heart and cardiac pulsations, and electrocardiogram are normal. Patients with valvular disease often complain of symptoms such as dyspnea and pain when physical examination fails to reveal evidence of heart failure.

White [1] states that in about one-fourth of all cases of angina pectoris, examination fails to reveal abnormality of the heart. Montgomery, Dry and Gage [2] report that in a series of 405 patients with angina pectoris due to coronary sclerosis, who survived for 10 or more years, electrocardiograms were normal in 236 (58.3 per cent). Scherf and Boyd [3] state that in early cases of coronary disease and angina pectoris the electrocardiogram taken in the ordinary manner is normal in nearly 60 per cent of the patients. In my own practice 37 per cent of the patients with angina pectoris proved to be due to coronary sclerosis possessed normal resting electrocardiograms. Hence the resting electrocardiogram in these cases was inadequate for diagnosis. Conversely, in investigating patients with chest pain and a normal electrocardiogram two-fifths were found to have organic heart disease. Despite the fact that the substernal pain suffered by these patients usually appears following effort, emotion, heavy meals, cold weather, or combinations of these factors, electrocardiograms are customarily made when the patients are in a resting state. Yet, from the physiological point of view, it is apparent that electrocardiographic indications of coronary insufficiency are more likely to become evident in tracings made following exercise than in those made when the patient is resting.

In cases of this type, a functional test, that is a test which obtains the response of the heart to effort, may be of great value in diagnosis and in evaluation of functional capacity. The "2-step" exercise test,[4] which was devised to provide such a test, has proved to be a reliable method of measuring cardiovascular function.

In addition to its value as a diagnostic aid in cardiac disease, the "2-step" exercise electrocardiogram test has proved useful in following improvement of patients during convalescence. It is a valuable aid also in the field of investigation.

Beginning in 1925, Enid T. Oppenheimer and the writer developed a

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test [4a] which utilized the response of the blood pressure and pulse rate to a standardized "2-step" exercise. This measure of vasomotor response was found to be a practical indication of circulatory fitness. Subsequently, it was found that the status of coronary circulation could be determined by electrocardiogram.[4c-4k] If coronary insufficiency existed, characteristic changes occurred in the electrocardiogram after standard exercise. When the coronary circulation was adequate no changes appeared in the electrocardiogram.[4e, f]

A complete review of the literature on the electrocardiogram following exercise will not be attempted in this paper as such reviews have been made by Feil and others [5-10] and in articles by my colleagues and myself.[4]

The "2-step" exercise test is a simple procedure. It consists of ascending and descending two 9-inch steps a variable number of times (depending

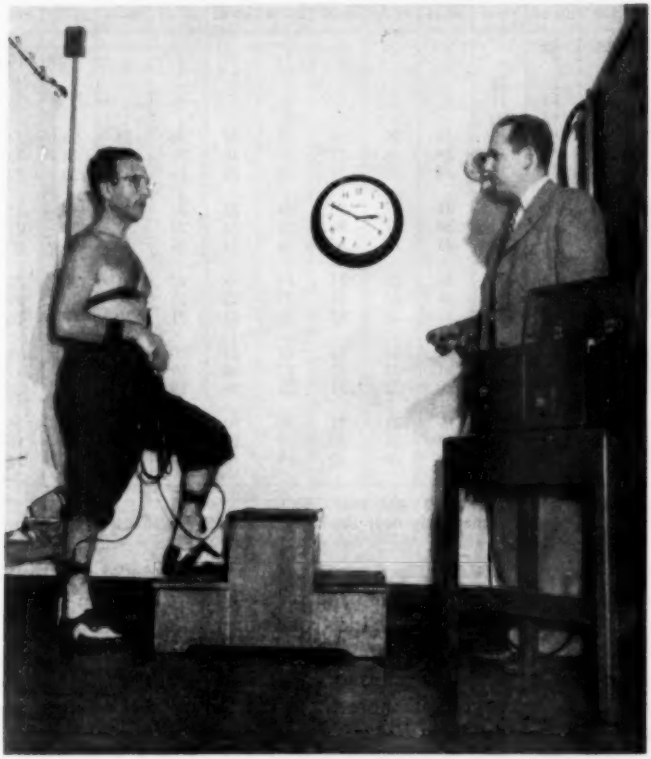

FIG. 1. Two steps each 9 inches high, placed against wall. Clock with sweep second hand for timing. Electrodes fastened on limbs and chest securely so that they are not loosened during climbing.

on age and weight) in one and one-half minutes. The accustomed nature of the work allays apprehension or excitement, thereby reducing psychic disturbance to a minimum. Even in these days of elevators, stair-climbing is so routine a type of work for everyone that it does not arouse mental reactions which, by increasing blood pressure and pulse rate, or which, by affecting the coronary circulation, may influence the very factors utilized in estimating the circulatory response to exercise. Since the "2-step" exercise is a sufficient test of cardiac function, as well as a natural type of effort, it may well replace tests which subject the patient to unnatural and excessive physical strain.

TABLE I

Standard Number of Ascents† for Males*

Weight (lb.)	Age in Years											
	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69
40–49	35	36											
50–59	33	35	32										
60–69	31	33	31										
70–79	28	32	30										
80–89	26	30	29	29	29	28	27	27	26	25	25	24	23
90–99	24	29	28	28	28	27	27	26	25	25	24	23	22
100–109	22	27	27	28	28	27	26	25	25	24	23	22	22
110–119	20	26	26	27	27	26	25	25	24	23	23	22	21
120–129	18	24	25	26	27	26	25	24	23	23	22	21	20
130–139	16	23	24	25	26	25	24	23	23	22	21	20	20
140–149		21	23	24	25	24	24	23	22	21	20	20	19
150–159		20	22	24	25	24	23	22	21	20	20	19	18
160–169		18	21	23	24	23	22	22	21	20	19	18	18
170–179			20	22	23	23	22	21	20	19	18	18	17
180–189			19	21	23	22	21	20	19	19	18	17	16
190–199			18	20	22	21	21	20	19	18	17	16	15
200–209				19	21	21	20	19	18	17	16	16	15
210–219				18	21	20	19	18	17	17	16	15	14
220–229				17	20	20	19	18	17	16	15	14	13

* Taken from Am. Heart J. **10**: 497, 1935.
† An ascent is one complete trip over the steps in one direction.

Numerous investigators have pointed out that excessive exertion causes electrocardiographic changes in normal persons.[6, 9, 11–13] One group of investigators [8] found changes in the electrocardiogram after their subjects had climbed 64 steps at a fast rate; and another [14] noted RS–T depressions immediately following one-mile runs or 30 minutes at squash. Because he obtained RS–T depressions in more than half the number of normal people who ran up 110 steps quickly Rosenberger [15] urged caution in the evaluation of the electrocardiogram following exertion and advised dependence on the history and clinical observations. Apparently it is not usually recognized that when a patient is required to make unusual or excessive effort, the

psychic, mental and physical reactions are unduly strong and consequently blood pressure, pulse rate, and electrocardiographic reactions are too pronounced to permit accurate estimation of cardiac function. Similarly, if the effort exerted is too slight, the electrocardiogram of even a person with coronary sclerosis may fail to register deviations from normal.

If exertion is to be measured accurately, the age and weight of the individual must be taken into consideration. A man weighing 200 pounds does more work climbing a step than one weighing 120 pounds, and a man who is 50 years old cannot expend as much effort as a man of 30, without undue strain. The figures in the standard tables for the "2-step" exercise,

TABLE II

Standard Number of Ascents† for Females*

Weight (lb.)	Age in Years												
	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69
40–49	35	35	33										
50–59	33	33	32										
60–69	31	32	30										
70–79	28	30	29										
80–89	26	28	28	28	28	27	26	24	23	22	21	21	20
90–99	24	27	26	27	26	25	24	23	22	22	21	20	19
100–109	22	25	25	26	26	25	24	23	22	21	20	19	18
110–119	20	23	23	25	25	24	23	22	21	20	19	18	18
120–129	18	22	22	24	24	23	22	21	20	19	19	18	17
130–139	16	20	20	23	23	22	21	20	19	19	18	17	16
140–149		18	19	22	22	21	20	19	19	18	17	16	16
150–159		17	17	21	20	20	19	19	18	17	16	16	15
160–169		15	16	20	19	19	18	18	17	16	16	15	14
170–179		13	14	19	18	18	17	17	16	16	15	14	13
180–189			13	18	17	17	17	16	16	15	14	14	13
190–199			12	17	16	16	16	15	15	14	13	13	12
200–209				16	15	15	15	14	14	13	13	12	11
210–219				15	14	14	14	13	13	13	12	11	11
220–229				14	13	13	13	13	12	12	11	11	10

* Taken from Am. Heart J. 10: 497, 1935.

† An ascent is one complete trip over the steps in one direction.

provide an exact measure of work performed. Such a measure is not possible with dumb-bell exercises, hopping, skipping, squatting and the like, which may be variously interpreted according to the intelligence, vigor and good will of the individual patient.

For convenience in performing the test we constructed a simple "two-step" contrivance made of three-quarters inch wood, with two steps on each side (figure 1). Each step is exactly 9 inches high and from 22 to 27 inches wide. The appearance of the apparatus does not cause foreboding, and the steps can be utilized as a seat or a shelf or placed out of the way under a table when not in use.

Tables * 1 and 2 give the number of climbs for age and weight.[4a, b, f, h] (In establishing the standards we found that height was not a factor when steps 9 inches high were used.)

Adequacy of the coronary circulation is revealed in the exercise electrocardiogram. Normal persons usually show no deviation following the exercise. Positive changes in the electrocardiogram [4f] (RS–T depressions, changes in the direction of the T-waves, and the like) are indications of coronary insufficiency. That the electrocardiographic changes following exercise are correlated with the oxygen supply of the heart muscle is shown by the fact that inhalation of mixtures of 10 per cent oxygen for 20 minutes may produce similar changes in the electrocardiogram. Exercise produces an oxygen debt.

Method

The procedure for obtaining electrocardiographic records in the "2-step" test is as follows: The electrodes are attached to the patient and his weight is recorded. He is then requested to sit down in a reclining chair or to lie on the examination table and to make himself comfortable. The number of times that he is to climb the "steps" is determined from the standard table (table 1). Next the electrocardiogram is taken. The technician or physician then demonstrates the procedure by climbing over the steps two or three times. The patient at a given command walks up one side of the steps and down the other, always turning to the same wall or side of the room before each ascent to prevent vertigo. He makes a trip only when he receives the count and the required number of ascents is completed in one and one-half minutes. If the patient climbs too slowly he is told to move more rapidly, if too fast, his ascents are made more deliberate. A stop watch, a wrist watch or electric clock with a sweep hand is used. At cessation of the exercise the patient sits down and the four leads of the electrocardiogram are recorded immediately. The electrocardiogram is then recorded at two and six minutes after cessation of exercise. Only a few beats in each lead are necessary.

* The figures presented in the tables are the result of thousands of tests made with several hundred normal men and women during the years 1925-1929 at Cornell University Medical College.[4a] The tests were repeated with each individual until we had determined the number of climbs he could make and have blood pressure and pulse return to within 10 points of the resting levels in two minutes. The work performed usually amounted to 1/8 of a horsepower for men and 1/11 of a horsepower for women. This is the average amount of work that engineers have found men and women are ordinarily able to do in the prime of life. The ability to expend energy within the limits designated in the standard tables appears to be inherent or fundamental in healthy men and women. Whether the patient is a laborer or sedentary person, whether he works indoors or outdoors, if his cardiovascular system is normal, pulse rate and blood pressure will return to within resting levels within two minutes of the end of exercise and the electrocardiogram will not change. It should be noted that when an athlete is in training he can make more than the standard number of climbs in the given period of time and yet have blood pressure and pulse rate return to resting levels. The electrocardiogram, however, does not reflect the result of training; that is, a man of 50 who has coronary disease has an abnormal electrocardiographic response following the 2-step exercise even though he may have been an athlete all his life.

Placing the steps near or against a wall gives a patient a sense of security. Further reassurance may be afforded by holding the patient's arm and guiding him over the steps, provided the examiner exerts no vertical lift.

Certain extracardiac factors * which may influence the electrocardiogram must be taken into account. Some drugs, such as thyroid extract and ephedrine affect the exercise tolerance. Alcoholic intoxicants or excessive smoking may have a similar effect. Distention of the stomach following a meal impairs the movements of the diaphragm; therefore the test should not be performed for at least one hour after a meal.[4, 17] An acute upper respiratory infection may be reflected in the electrocardiogram. Perhaps more important than any of the factors just mentioned are the changes induced in the electrocardiogram by intense excitement or emotion. (Slight excitement, emotion, or nervousness will not affect the results.[18, 19]) An attempt therefore should be made to put the patient at ease. The "resting" electrocardiogram may be taken in either a sitting or a lying position, provided the patient returns to the same position after exercise.[4, 16, 20] The room in which the test is performed should be neither too quiet, nor too noisy; rather there should be an atmosphere of reassurance and of ordinary life. The patient is shown how to do the test for two or three trips. He is assured that the test is entirely harmless but that if he develops any untoward symptoms he may stop. Pain or shortness of breath are very seldom engendered by the test. A man who cannot walk 50 feet out-of-doors without stopping because of chest pressure, will have no symptoms during or following the "2-step" exertion, except on the rarest occasions. It may be that walking outdoors, or climbing a flight of stairs produces a sort of conditioned reflex, but patients who cannot take such exercise without discomfort, perform the "2-step" exercise with relative ease and equanimity.

In interpretation of the electrocardiogram, the P–R interval is taken as the control level. Depression of the RS–T segment of over 0.5 mm. in any lead is considered a positive result. In other words, the level of the string just following the QRS complex, is compared with that immediately preceding the complex. In a series of tests made for the Public Health Service, Malmo and his colleagues [21] found that RS–T depressions did not occur in normal persons. Battro,[22] also, found that the "2-step" exercise did not produce electrocardiographic changes in normal subjects. However, to be conservative, an RS–T depression less than 0.5 mm. below the P–R level is not considered abnormal for the test.

A change from an upright T-wave to an isoelectric (flat) or inverted T-wave is also an abnormal response; so, too, is a change in the other direction, that is, from a flat or negative, to a positive T-wave. Occasionally, premature beats or some more significant arrhythmia, widening of the QRS, intraventricular or bundle branch block, large Q-waves, prolongation of the P–R interval, or heart block may appear. All of these are considered abnormal responses to the exercise. A change from an inverted or flat T-wave to an upright T-wave is abnormal. Although this may appear paradoxical,

* Among the extracardiac factors which influence the electrocardiogram, Sensenbach [16] includes the following: digitalis, quinidine, quinine, atabrine, plasmochin, adrenalin, atropin, mecholyl, emetine, tobacco, exercise, infections, pericarditis, metabolic disorder, renal disease, visceral disease, pancreatitis, gall-bladder, ulcer, autonomic nervous system imbalance.

clinical experience has proved that such a reaction is not normal. The same type of change has been seen during the 10 per cent anoxemia test. For example, in the electrocardiogram of a patient with coronary disease a T_1 that is inverted before the test, becomes upright as the patient becomes anoxemic, even cyanotic, with chest pain.

A change from an inverted T-wave to an upright wave in Lead III alone is not a positive result since this is frequently observed in normal persons. (Perhaps it is because the diaphragm becomes depressed during or shortly following exertion.)

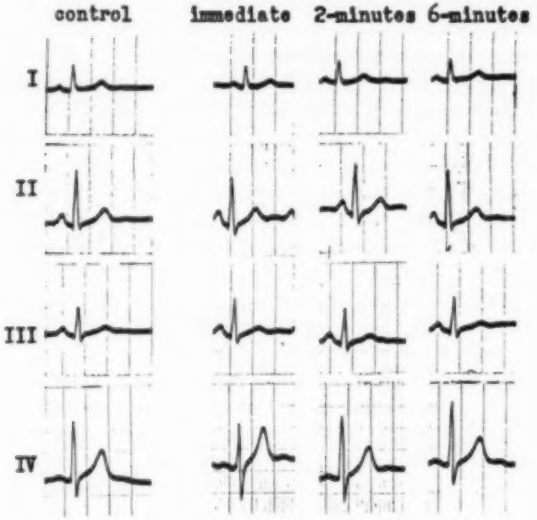

FIG. 2A. A man 49 years old with chest pain, not related to exertion. Put to bed with a diagnosis of acute coronary occlusion. Control electrocardiogram normal and remained negative after "2-step" exercise.

A follow-up of many of our patients confirmed the accuracy of the electrocardiographic findings in the "2-step" test. Battro [22] made similar observations, as have various other authors. Donovan [23] had occasion to evaluate a chest complaint in a patient with mediastinal tumor. The electrocardiogram following the "2-step" exercise was positive and subsequent postmortem examination disclosed extensive coronary disease with the lumen almost obliterated. Feil and Pritchard [10] found the "2-step" electrocardiogram of value. Other investigators [6, 12] reported the exercise electrocardiogram of help in diagnosing a doubtful case of angina pectoris.

A few case histories will be cited to illustrate the points made hitherto and to demonstrate the diagnostic value of the "2-step" exercise test.

Case 1. A man 49 years old was seen in consultation August 20, 1947. Two days before, he had experienced pain in the lower left chest, which was so severe that morphine was administered twice. A diagnosis of acute coronary occlusion was made. Physical examination of the heart and lungs was entirely normal. An electrocardiogram, including limb, unipolar extremity and precordial leads, was entirely negative.

On questioning the patient it was found that the patient had suffered similar pain twice in the preceding year and that he had quickly recovered and played "singles" at tennis the following day or two. Since blood counts, temperature readings, sedimentation rates, urine analyses were all normal the family physician was persuaded to allow the patient to undergo a "2-step" exercise test August 22, 1947 (figure 2A). The control tracing and the tracings following the "2-step" exercise were normal.

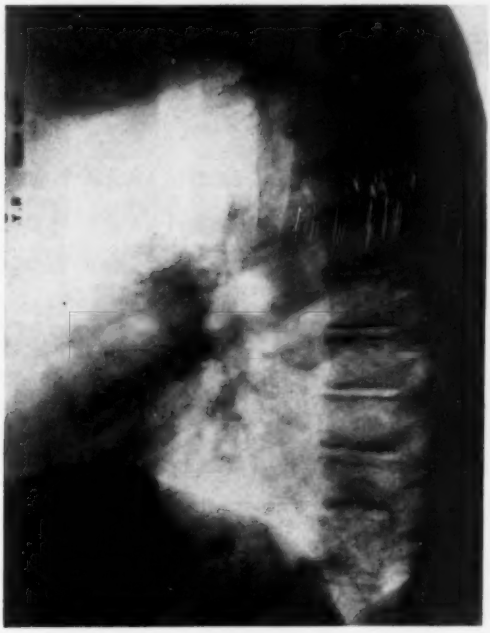

FIG. 2B. X-ray of spine shows a definite hypertrophic spondylitis with "lipping, spur formation and bridging."

Because of the atypical story of chest pain and the negative "2-step" electrocardiogram the heart was ruled out as a source of the precordial pain and so x-ray films were taken of the dorsal spine (figure 2B). The roentgenologist reported "a definite hypertrophic spondylitis with lipping, spur formation and bridging between the upper dorsal and the lower dorsal [9, 10, 11] vertebrae." An x-ray study of the gall-bladder, stomach and duodenum, including search for a hiatus hernia, was without any positive results.

Comment: Heart disease as the source of severe lower left chest pain was disproved by a negative "2-step" electrocardiogram. The past history, which disclosed the ability of the patient to play hard a day or two following severe chest pain, and the discovery of a severe lower dorsal spondylitis confirmed the value of the "2-step" electrocardiogram.

Case 2. A 46 year old man experienced frequent heart attacks for 20 years which were diagnosed as angina pectoris due to coronary disease in spite of his relatively young age. The attacks were unrelated to activity and consisted of substernal pain and pressure radiating to the left shoulder and arm, lasting several hours. Seven months before, following a severe attack of pain, he was hospitalized for six weeks and treated for "acute coronary occlusion." Weekly attacks of pain continued thereafter. Repeated electrocardiograms in the past were normal. During the past two years the patient also experienced epigastric pain one hour after meals, relieved by milk and alkalies. A gastrointestinal x-ray series had revealed a duodenal ulcer.

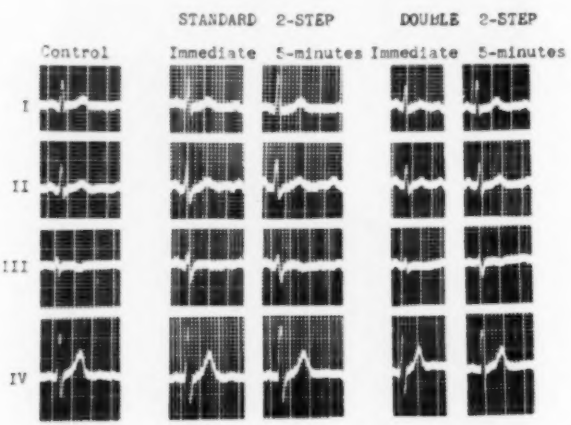

FIG. 3A. A man of 46 with attacks of substernal pain radiating to left arm for 20 years. No objective evidence of cardiac disease. Standard and double "2-step" tests negative.

Physical examination of the cardiovascular system when the patient came under our observation was negative. Roentgenographic examination of the stomach revealed a hiatus hernia of moderately large size (figure 3A) and a markedly deformed duodenal bulb. The heart was normal in size and configuration and the ventricular pulsations were observed fluoroscopically to be normal. The electrocardiogram, including multiple precordial leads, was entirely normal. No significant change occurred following the "2-step" exercise, utilizing both the standard and the double number of trips (figure 3B).

The negative standard and double "2-step" exercise electrocardiograms proved coronary disease to be absent. This conclusion was corroborated by the absence of objective evidence of any heart disease in a man with a 20 year history of attacks simulating angina pectoris and the discovery of a hiatus hernia which explained the pain in the chest and left arm. Further-

more, the pain was not typical of angina pectoris since it was unrelated to effort, was relieved by rest only after 15 to 20 minutes, often lasted for several hours and infrequently responded to nitroglycerin. The so-called "attack" of coronary thrombosis was in all probability an episode of pain secondary to the hiatus hernia.

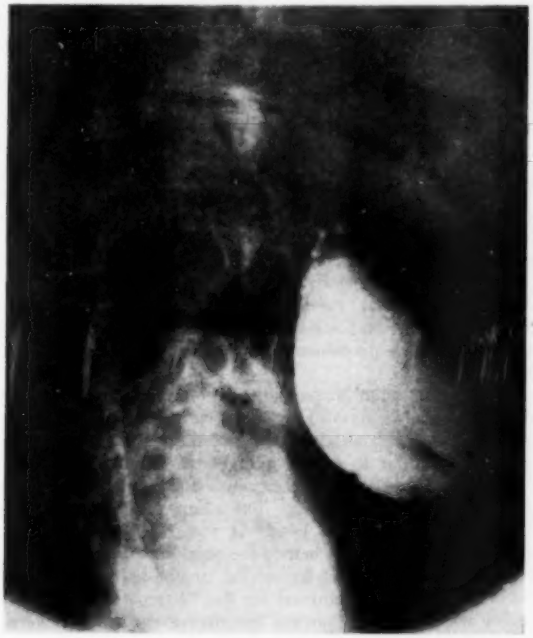

FIG. 3B. Large hernia on x-ray examination.

Case 3. A man of 60 gave a history of epigastric pain and gastrointestinal bleeding for several years for which he was hospitalized twice in the city hospitals of New York and a diagnosis of duodenal ulcer made. In January 1947 he was admitted to the Mount Sinai Hospital, New York, because of syncopal attacks associated with pressure over the lower portion of the chest which radiated to the back. There was shortness of breath on exertion. Physical examination was normal. Because of the syncope the diagnosis was considered to lie between a cerebral lesion and a bleeding duodenal ulcer but coronary disease was not suspected since the resting electrocardiogram was normal. However, no evidence of bleeding could be discovered and the stool examination was negative. The neurological examination was normal. When the patient was seen in consultation a "2-step" exercise electrocardiogram was advised. It proved to be strongly positive (figure 4A). Distinct RS–T depressions and T-wave inversions appeared in Leads I, II and IV and a diagnosis of coronary artery sclerosis was made. This was confirmed by the 10 per cent oxygen test (figure 4B) which disclosed conspicuous depressions of the RS–T segment also in Leads I, II and

IV. Subsequent events further established the specificity of the "2-step" exercise. The patient developed a classical anginal syndrome, i.e., substernal pressure on effort or excitement and then suffered an acute coronary occlusion October 1947. The last tracing, taken January 5, 1948, showed large Q-waves in Leads II and III and depression of the RS–T intervals in all the leads; it was made during a spontaneous episode of angina pectoris.

This case demonstrates that the "2-step" exercise test disclosed the only objective evidence of coronary disease and the 10 per cent oxygen test and subsequent clinical and electrocardiographic follow-up proved its validity.

Case 4. A 63 year old man was first seen in consultation November 27, 1946. For nine years he had experienced choking pain in the throat brought on by effort and excitement. Walking one block and talking on the telephone were precipitating causes. Nitroglycerin was taken 10 to 15 times a day. In the last few years, previous to November 1946, he had been told by numerous consultants that his pain was on a neurotic basis because of the normal electrocardiograms and the absence of other objective evidence of organic heart disease. He was indeed a nervous, energetic, fast-talking, tense person. He was intelligent above the average, an able linguist and his profession was that of interpreter.

Physical examination was negative. The man was well built. The heart was not enlarged, the rhythm regular, the blood pressure normal. The teleroentgenogram of the chest disclosed a heart and aorta of normal size, shape and position for a man of 63. The aortic knob was prominent. The cardiac contractions were normal on fluoroscopic investigation.

An electrocardiogram, taken November 23, 1946, including the unipolar extremity and the unipolar precordial leads V–1 to V–6, was negative. The rate of the heart was 75 beats per minute; a left axis deviation of the QRS group was present (figure 5). This tracing was similar to earlier control tracing on April 1946. A "2-step" exercise test was about to be performed but while the control tracing was being taken the patient developed upper chest pain. The electrocardiogram (figure 5) showed depression of the RS–T segment in Leads II and III, November 27, 1946. Three nitroglycerin tablets had to be taken before the pain was relieved. The patient rested until his electrocardiogram returned to normal in one-half hour.

Three days later the patient returned for the "2-step" exercise electrocardiogram. The control tracing was practically normal but after exercise there were distinct RS–T depressions, particularly noticeable in Leads II and IV.

A diagnosis was made of a severe case of angina pectoris due to coronary artery disease and the importance of a let-up, mentally and physically was stressed. The family physician was informed that because of the severity of the patient's condition paravertebral block was to be seriously considered.

On December 4, 1946, at 10 p.m., the patient developed severe precordial pain, went into a shock-like state and was removed to the reception ward of the Mount Sinai Hospital. An electrocardiogram showed regular sinus rhythm, rate 75 beats per minute, with conspicuous depressions of the RS–T segment in Leads I, II and IV. The patient did not rally in spite of emergency treatment and died within a few hours.

At postmortem examination severe arteriosclerosis of the coronary arteries was discovered with diffuse myocardial fibrosis concentrated chiefly in the subendocardial region.

Summary: A 63 year old man with a history of chest pain on effort for nine years was thought to be a hysterically neurotic person because physical examination and objective tests made while at rest revealed no abnormality. The "2-step" electrocardiogram disclosed RS–T depression and T-wave in-

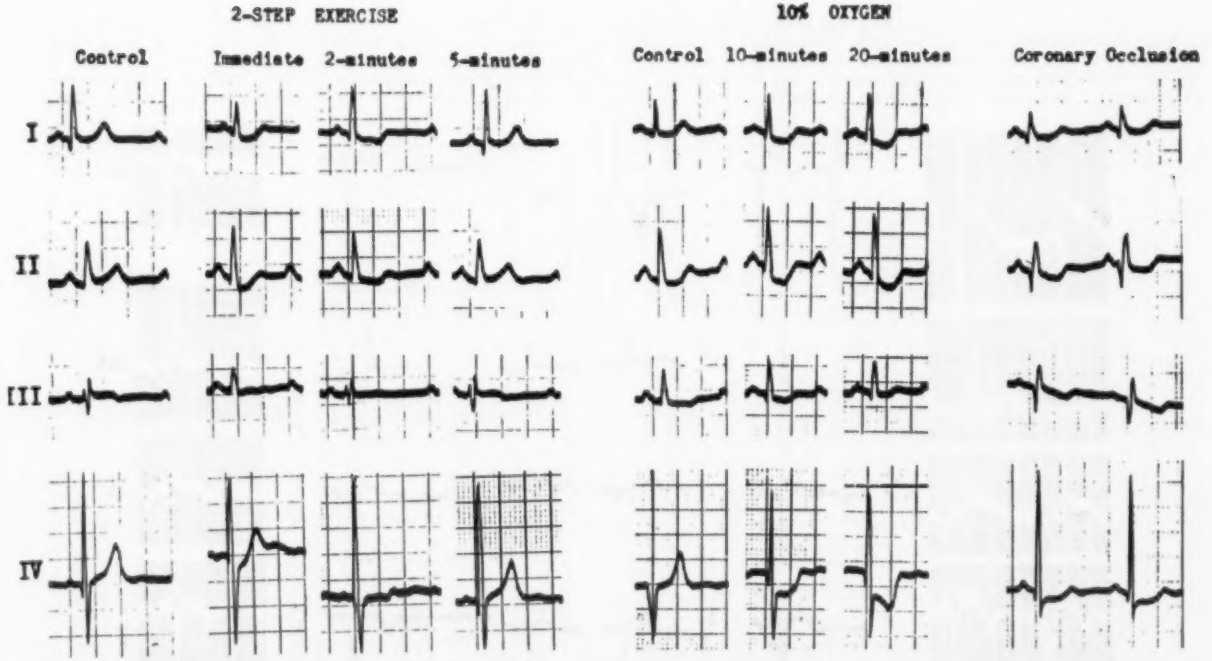

FIG. 4. A 61 year old man with "syncope" and chest pressure. Cardiovascular examination entirely negative, including control resting electrocardiogram. Following the standard "2-step" exercise, abnormal RS-T segment depressions and T-wave inversions appeared. A 10 per cent oxygen test showed a negative control resting electrocardiogram but the appearance of RS-T depression and T-wave inversion during the test. Further corroboration of positive "2-step" exercise electrocardiogram was obtained by the spontaneous coronary occlusion a few months later.

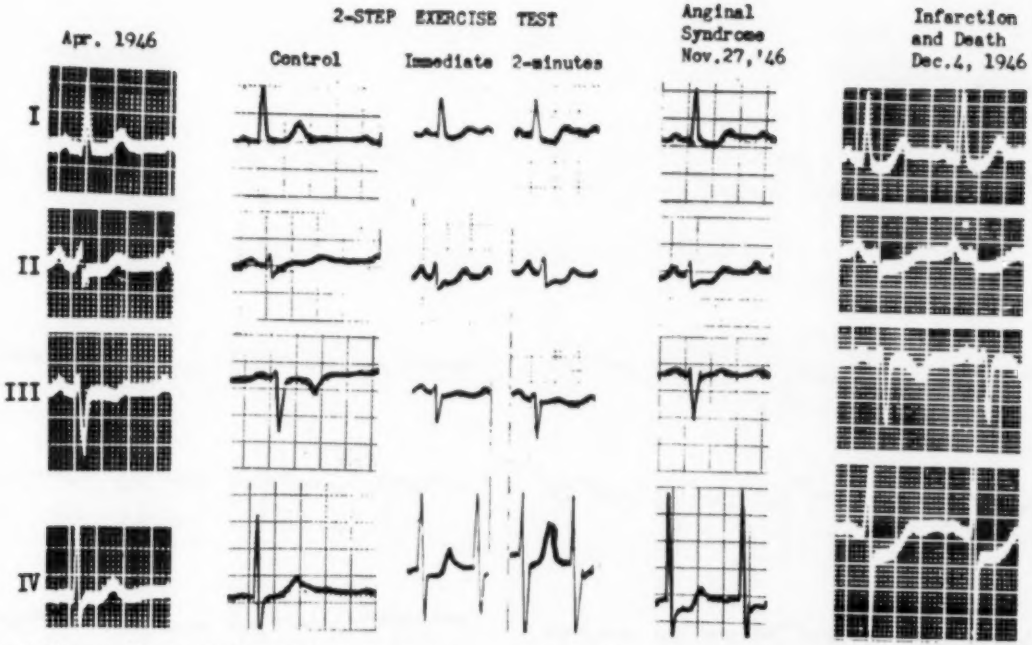

FIG. 5. A 63 year old man with a typical anginal syndrome for 9 years. Normal resting electrocardiogram, April 1946. Standard "2-step" exercise test November 1946 showed normal control electrocardiogram but abnormal RS–T depressions and T-wave inversions. A spontaneous attack of angina pectoris November 27, 1946, disclosed similar electrocardiographic changes, thus confirming the value of the exercise tolerance. Final proof of severe coronary disease was obtained in a postmortem examination December 4, 1946 following an attack of severe chest pain, collapse and death. The electrocardiogram here too revealed conspicuous RS–T depressions.

versions demonstrating for the first time the serious coronary sclerosis from which the patient suffered. The electrocardiogram during a spontaneous attack of angina pectoris was similar to that following the standard "2-step" exercise. Finally, the value of the "2-step" exercise electrocardiogram was more than confirmed by a severe attack of acute coronary insufficiency and death. Postmortem examination disclosed severe coronary arteriosclerosis.

Discussion

The "2-step" exercise test is a reliable gauge of cardiac function only if the standardized exercise is carried out with exactitude. When a patient with a history of angina pectoris is permitted to walk at a rate that he chooses or until he develops symptoms the electrocardiogram cannot properly be compared with the one made following the "2-step" exercise. Knee-bending has been employed [6, 9] but this is a formidable type of exertion, an unaccustomed procedure, therefore difficult to evaluate quantitatively. Similarly, the so-called "step-up" test which makes use of a single step 15, 18 or 20 inches in height is an unusual and strenuous climb for most patients. The tall man has a conspicuous advantage but the average sized, short or fat person finds it difficult physically. Because of this, strong emotional reactions may be produced which may affect the electrocardiogram.

The T and RS–T alterations that occur in electrocardiograms following the "2-step" exercise are qualitatively the same as similar changes observed in anoxemia. Many writers [3, 5, 24–27] have recorded the electrocardiographic changes in anoxemia. A number of authors point out that quantitatively also, electrocardiographic changes produced by the "2-step" exercise are like those caused by the 10 per cent oxygen test.[41, 21] Malmo and Baum [21] found that in normal persons, the "2-step" exercise and the 10 per cent anoxemia test gave the same electrocardiographic picture. Not only anoxemia, but metabolic disturbances in the cardiac muscle have been cited to explain the changes in the electrocardiogram.[2]

As we have already pointed out, coronary insufficiency is reflected in the electrocardiograms after the "2-step" exercise irrespective of the patient's customary activity. Even a high degree of previous physical training does not alter the result.

It is apparent that the "2-step" exercise test is of value chiefly when the resting electrocardiogram is normal. Obviously, if this electrocardiogram is abnormal an exercise test is unnecessary.

Patients are not fatigued by the "2-step" exercise. The work is simple, practical and of short duration. During the performance of many hundreds of tests, we have never observed untoward incidents. Even moderately ill patients who regularly suffer pain or pressure in the chest when climbing a full flight of stairs or walking half a small city block or entering a cold environment, can do the "2-step" exercise without difficulty. Occasionally, a patient with a severe anginal syndrome due to coronary disease or due to

a "tight" mitral stenosis will be unable to perform more than seven or eight trips.

Accidents following exercise tests have been reported in the literature.[28] It is to be observed that in these cases either the "2-step" exercise was not used, or our exact technic was not followed. Moreover, if it is insisted that the resting electrocardiogram be normal before exertion is attempted, added assurance is thus obtained.

It is not the purpose of the "2-step" test to induce angina. We agree with Wilson [28] that it is unwise to induce attacks of chest pain for diagnostic purposes. In the presence of coronary disease the electrocardiographic changes are the same, whether or not pain or pressure occurs during exercise.[4, 6, 12, 22, 29] Moreover the results are not altered if the exercise is stopped because of chest pressure. In such cases the test is usually positive. Of further interest is the fact that the electrocardiographic changes produced by the "2-step" exercise are similar to those seen in a spontaneous attack of angina. This has also been observed in the electrocardiograms made following knee-bending exercise,[6] and we have discovered this similarity in the "2-step" test.

It is known that hyperventilation [30, 31] produces alterations in the electrocardiogram. Ungerleider, Duhigg and Gubner [31] believe this to be the explanation for the changes that occur following the "2-step" exercise. However, although the exertion requires effort on the part of the patient, it does not induce hyperventilation; the patient may breathe a little harder momentarily. Even when dramatic deviations appear on the electrical tracing, the patient does not experience discomfort. Hyperventilation may occur rarely in a mentally ill patient who is suffering from an anxiety state.

Should a negative "2-step" exercise electrocardiogram be accepted as a reliable indication of adequate coronary circulation? I believe there is sufficient supporting evidence to justify acceptance of the test and I practically exclude coronary insufficiency, organic or functional, if two tests are negative. At first, the single "2-step" is performed and if the electrocardiogram remains normal then a double "2-step" is done, i.e., twice the usual number of trips in three minutes instead of one and one-half minutes. Other authors,[3] too, consider that there is no marked disturbance of the coronary blood supply if the exercise electrocardiogram is negative. Conversely, should a positive "2-step" test be accepted as evidence of coronary insufficiency? Coronary insufficiency exists if the electrocardiogram following the "2-step" exercise is positive. A positive exercise electrocardiogram has been considered pathognomonic of interference with coronary circulation.[3] However, it is not necessarily a sign of organic coronary disease; the insufficiency may be functional. Patients who are under a great deal of mental or emotional tension and those suffering from anxiety neuroses or from severe neurocirculatory asthenia may have positive "2-step" electrocardiograms. The effect of emotion on the heart and the electrocardiogram has been emphasized by a number of authors.[18, 32, 34] Furthermore, as noted before, many

extracardiac or functional conditions may present changes in the exercise electrocardiogram [10] and produce positive changes in the 10 per cent oxygen test.[35] In the vast majority of cases, the differential diagnosis is not difficult. Other writers [6, 12] also found that positive electrocardiograms following exercise were not necessarily an indication of organic heart disease.

The "2-step" exercise test lends itself to the field of investigation.[4, 22, 36] Thus it permits quantitative classification of the myocardial reserve of patients with valvular disease. The effect of mitral and aortic lesions on the coronary circulation may be compared. Similarly the exercise electrocardiogram may discover coronary osteal stenosis in syphilis when there is no apparent involvement. Thus Berk [36] found electrocardiographic changes in apparently normal cardiovascular systems in patients with syphilis 12 times more frequently than in non-syphilitic patients. In other words, there was involvement of the coronary ostia in the patients with syphilis. Does exercise tolerance correspond to the size of the heart rather than to the nature of the valvular lesion? What are the quantitative limits of exercise for patients with anginal syndrome, essential hypertension, exophthalmic goiter? Occasionally, patients recovering from acute infections complain for as long as three to six months, of dyspnea on the slightest exertion, fatigability, weakness or rapid pulse. Gore and Saphir [37] have emphasized the occurrence of acute myocarditis in acute disease. The exercise electrocardiogram of such patients has been found to be abnormal. Simultaneously with increase in work capacity, as indicated by the "2-step" test, the symptoms have disappeared. The "2-step" exercise electrocardiogram may be used in studying patients with acute and chronic anemias. It also provides useful information of the patient's condition following hemorrhage, following injection of insulin, adrenalin, and pituitrin, the administration of vasodilator drugs, and following smoking. Proger and Dekaneas [38] found the "2-step" test useful for objective evaluation of results of administration of cytochrome C to patients with angina pectoris. Other drugs and preparations used for the relief of angina pectoris, such as aminophyllin, theobromine, vitamins, sex hormone injections can be similarly evaluated. Nitroglycerin administered to patients with angina pectoris before exertion has been found to prevent the electrocardiographic changes that ordinarily follow exertion.[6]

The "2-step" electrocardiogram can be used in the study of coronary circulation in patients with hypertension. A great many patients with hypertension live for years without evidence of coronary insufficiency, and their resting and their exercise electrocardiograms remain normal. Other subjects for research include patients with chest deformities, with diaphragmatic hernia, and circulatory complications following operations. For example, the "2-step" test affords a means of differentiating the substernal pain caused by diaphragmatic hernia and that caused by coronary disease [39]; in cases of diaphragmatic hernia, the electrocardiogram remains normal, whereas coronary disease produces alterations.

Electrocardiograms made in conjunction with the "2-step" exercise serve

to measure improvement in a patient's condition during convalescence from cardiac attacks. Following coronary occlusion, a patient's resting electrocardiogram may return to normal while the "2-step" electrocardiogram will register abnormalities. As improvement continues, however, the exercise electrocardiogram becomes normal. The exercise electrocardiogram of a patient with coronary insufficiency may lose its abnormalities as the patient recovers from the attack.[40]

Our criteria of abnormality in the "2-step" exercise electrocardiogram, that is, depression of the RS–T segment of more than 0.5 mm. in any lead, has been questioned by some authors. Duchosal and Henny [12] believe that there should be RS–T depression of 1 mm. or more before the tracing is considered to be normal. Biörck [41] also believes that our criteria of abnormality are too liberal. It is to be pointed out, however, that by RS–T depression we mean definitely a lowering below the baseline, i.e. below the P–Q or P–R interval. In normal persons a slightly elevated RS–T segment not infrequently will be lowered to the isoelectric level. This we do not interpret as an abnormality whereas many investigators do. Actually, our criteria are really more conservative than theirs.

In a patient with an anginal syndrome, exercise tolerance may be the only objective evidence of myocardial impairment. In the malingerer the "2-step" exercise electrocardiogram will be normal.

The "2-step" exercise test, quick and simple as it is, is useful in yearly examinations, particularly of men and women 35 years of age or over. In health examinations it is not enough to take a resting electrocardiogram but rather the person must be made to exercise if his tracing is normal.

Since the electrocardiographic changes often occur only immediately following exercise, the four leads should be obtained quickly. An experienced technician can take the four leads in from 15 to 30 seconds; 40 seconds is ample time. At least two or three heart beats should be registered on the same horizontal level, as, otherwise, artificial changes in the RS–T level occur. In our procedure an electrocardiogram is taken immediately following cessation of exercise and repeated at the end of two minute and six minute intervals. Some investigators take an electrocardiogram at the end of 10 minutes.

The chest lead is very valuable and at least one, preferably V_4 or CF_4 should be taken.[4b, 5, 29, 42] The chest lead is probably more frequently positive than any of the standard leads. Moreover, the deviations in this lead are larger quantitatively, as a rule.

We believe that studies being carried on at present will afford evidence that the "2-step" electrocardiogram is occasionally interchangeable with the 10 per cent oxygen test. The physiological effect of the "2-step" test may be the same as that produced by taking the patient to an altitude of 18,000 feet for a moment or two. Since all patients with the exception of the most seriously ill can perform the "2-step" exercise without harmful effects, the question arises whether or not patients with coronary disease should be permitted to make flights in which the plane may reach a level of 8,000 or

10,000 feet. I allow my patients with heart disease to make such flights provided they understand that they are to remain quiet, not to exert themselves on the plane, and not to eat large meals. I have found that when these conditions are complied with, adverse effects are not experienced. If the patient is subject to air-sickness, I prohibit the trip. If the plane keeps at 10,000 feet level for any length of time, or if it goes higher, oxygen may be required. To meet this contingency, I advise patients to learn beforehand whether oxygen is available on the plane. Graybiel [43] noted that when patients with severe coronary disease were at rest, they could tolerate great reduction in oxygen tension. The "2-step" exercise electrocardiogram should prove of value in the examination of potential pilots or in the regular examination of experienced pilots. Pilots suffering from unsuspected coronary disease have had fatal accidents.[44]

RS–T depressions, not RS–T elevations, are found in patients with coronary insufficiency. The explanation for the depression has been given in previous papers [45]; it is because the subendocardial region is more susceptible to anoxemia than the epicardium. Lesions—functional or anatomic—in the subendocardium produce RS–T depressions, those in the epicardium produce elevations. The subendocardium feels the lack of oxygen so readily for many reasons. Among these is the fact that it is farthest from the source of the coronary blood supply. During systole of the left ventricle, especially during the isometric phase, the intramural pressure is highest beneath the endocardium and least beneath the pericardium.

RS–T elevations, particularly in Lead III or in Leads II and III, occasionally occur following the "2-step" exercise. This abnormality is almost invariably observed in patients who have a large Q_3 or a large Q_3 and Q_2 in the resting electrocardiogram. In other words, these RS–T elevations occur in persons in whom the posterior or diaphragmatic surface of the left ventricle is particularly susceptible to anoxemia. A study of the control tracings in the reports describing RS–T elevations supports this observation.[6, 7, 46–48]

Even rarer than the occurrence of RS–T elevations after the "2-step" exercise in Lead III or in Leads II and III is its appearance in Lead I or precordial leads. Recently we saw such an instance in a man who had suffered a previous coronary occlusion involving the anterior surface of the left ventricle. There was a large Q-wave in Lead I. So again, RS–T elevations may appear if the anterior wall of the left ventricle is peculiarly sensitive to anoxemia. Finally a very rare RS–T elevation is found in the electrocardiogram after exercise without apparent explanation. There may be an aberrant coronary circulation to the myocardium causing the subepicardium to be particularly prone to anoxemia.

Recently Ruskin [49] proposed a pitressin test for coronary insufficiency. He injects 2 c.c. of pitressin intramuscularly or 0.75 c.c. intravenously. Alterations in the electrocardiogram are due to the constrictural effort of the drug on the coronary arteries. Ruskin used this test on patients whose resting electrocardiograms were abnormal, and therefore a basis for com-

parison of this test and the "2-step" test is not available. It should be kept in mind that administration of pitressin may be accompanied by undesirable side reactions. Proper evaluation of the test must await further investigation. Ruskin states that pitressin is not suitable for general use because of undesirable side reactions.

Summary

The diagnosis of heart disease is often complicated by the fact that objective evidence of organic disease cannot be obtained. Physiologically, electrocardiographic indications of coronary insufficiency are more likely to become evident in tracings made following exercise than in those made when the patient is resting.

The "2-step" exercise test obtains the response of the heart to effort and the status of the coronary circulation can be determined by this exercise electrocardiogram.

The "2-step" exercise test is a simple procedure. The accustomed nature of the work allays apprehension or excitement.

The exertion must be standardized and tables must give the number of climbs for age, weight and sex. The exercise electrocardiogram does not reflect the result of previous physical training. It is a reliable gauge of cardiac function only if the standardized exercise is carried out with exactitude.

Depression of the RS–T segment of over 0.5 mm. in any lead below the isoelectric level is considered a positive result. A change from an upright T-wave to an isoelectric (flat) or inverted T-wave is also an abnormal response except Lead III.

The "2-step" exercise test is chiefly of value when the resting electrocardiogram is normal. If the resting tracing is abnormal the exercise test is unnecessary.

Patients are not fatigued by the "2-step" exercise. It is not the purpose of the "2-step" test to induce angina but the electrocardiographic changes are the same whether or not pain or pressure occurs during exercise. The electrocardiographic alterations are similar to those seen in a spontaneous attack of angina pectoris.

The alterations in the electrocardiogram are not produced by hyperventilation. Hyperventilation does not ordinarily appear following the "2-step" effort.

Coronary insufficiency is practically excluded if two tests are negative, a standard and then a double "2-step." The latter consists of a continuation of the climbs for another minute and a half.

Coronary insufficiency exists if the electrocardiogram following the "2-step" exercise is positive. However, it is not necessarily a sign of organic heart disease; the insufficiency may be functional. Extreme mental or emotional tension may produce a positive "2-step" electrocardiogram. In the majority of cases the differential diagnosis is not too difficult.

In a patient with anginal syndrome exercise tolerance may be the only

objective evidence of myocardial impairment. The malingerer has a normal "2-step" exercise electrocardiogram.

The "2-step" exercise, short and simple as it is, is useful in yearly examinations. It should prove of value in the examination of potential pilots or in the regular examination of experienced pilots.

The "2-step" exercise test lends itself to the field of investigation.

Certain extracardiac factors influence the electrocardiogram and must be taken into account.

The electrocardiogram in the 10 per cent oxygen test, if it reveals deviations from the normal, is similar to that in the "2-step" exercise. In such cases the physiological effect of the "2-step" exercise is to take one to an altitude of 18,000 feet for a moment or two.

The chest lead is probably more frequently positive than any of the standard limb leads and the deviations in this lead are larger quantitatively, as a rule.

RS–T depressions (very rarely RS–T elevations) are observed in patients with coronary insufficiency. The depressions result because the subendocardial region of the heart is more susceptible to anoxemia than the subepicardial. By depression is meant a lowering of the RS–T segment below the baseline, i.e., the P–Q or P–R interval.

BIBLIOGRAPHY

1. White, P. D.: Heart disease, 3rd ed., 1944, Macmillan Co., New York, p. 827.
2. Montgomery, G. E., Jr., Dry, T. J., and Gage, R. P.: Further observations on the prognosis in angina pectoris due to coronary sclerosis. A study of 405 patients who survived ten or more years, Minnesota Med. **30**: 162, 1947.
3. Scherf, D., and Boyd, L. J.: Clinical electrocardiography, 2nd ed., 1946, Lippincott, Philadelphia, p. 110.

4a. Master, A. M., and Oppenheimer, Enid T.: A simple exercise tolerance test for circulatory efficiency with standard tables for normal individuals, Am. J. M. Sc. **177**: 223, 1929.

b. Master, A. M.: The two-step test of myocardial function, Am. Heart J. **10**: 495, 1935.

c. Master, A. M., and Jaffe, H. L.: The electrocardiographic changes after exercise in angina pectoris, J. Mt. Sinai Hosp. **7**: 629, 1941.

d. Master, A. M.: The electrocardiogram after exercise; a standardized heart function test, U. S. Nav. M. Bull. **40**: 346, 1942.

e. Master, A. M., Carroll, H. H., and Andrews, C.: Coronary insufficiency and coronary occlusion, U. S. Nav. M. Bull. **40**: 810, 1942.

f. Master, A. M., Friedman, R., and Dack, S.: The electrocardiogram after standard exercise as a functional test of the heart, Am. Heart J. **24**: 777, 1942.

g. Master, A. M., Dack, S., and Jaffe, H. L.: Cardiac efficiency and prognosis following recovery from acute coronary occlusion; the results of various functional tests, J. A. M. A. **120**: 1271, 1942.

h. Master, A. M.: The electrocardiogram and the two-step test of cardiac function and coronary insufficiency, Naval Medical School, National Naval Medical Center, Bethesda, Md., Feb. 1943.

i. Master, A. M., Nuzie, H. C., Brown, R. C., and Parker, R. C., Jr.: The electrocardiogram and the "two-step" exercise. A test of cardiac function and coronary insufficiency, Am. J. M. Sc. **207**: 435, 1944.

j. Master, A. M.: Neurocirculatory asthenia due to small heart, M. Clin. North America **28**: 577, 1944.

k. Master, A. M., Weintraub, H. J., and Gertler, M. M.: The "two-step" and the "anoxemia" tests. Case report of a patient with coronary artery disease and normal electrocardiogram, J. Mt. Sinai Hosp. **15**: 21, 1948.

5. Feil, H.: The chest lead electrocardiogram in chronic cardiac anoxemia, *In* Pub. Am. Ass. Adv. Sc., no. 13, Blood, Heart and Circulation, pp. 163–169, 1940.

6. Scherf, D., and Goldhammer, S.: Zur Frühdiagnose der Angina pectoris mit Hilfe des Elektrokardiogramms, Ztschr. f. klin. Med. **124**: 111, 1933.

7. Hausner, E., and Scherf, D.: Über Angina pectoris—Probleme, Ztschr. f. klin. Med. **126**: 166, 1933.

8. Riseman, J. E. F., Waller, J. V., and Brown, M. G.: The electrocardiogram during attacks of angina pectoris: its characteristic and diagnostic significance, Am. Heart J. **19**: 683, 1940.

9. Laurentius, P., and Klopffleisch, F.: Kreislauffunktionsprüfung bei Wehrmachtangehörigen unter besonderer Berücksichtigung des Belastungs-Elektrokardiogramms, München. med. Wchnschr. **87**: 1045, 1940.

10. Feil, H., and Pritchard, W. H.: The electrocardiogram of anginal attacks induced by exercise, Mod. Concepts Cardiovas. Dis. **15**: No. 4, April, 1946.

11. Wood, F. C., and Wolferth, C. C.: Angina pectoris; the clinical and electrocardiographic phenomena of the attack and their comparison with the effects of experimental temporary occlusion, Arch. Int. Med. **47**: 339, 1931.

12. Duchosal, P. W., and Henny, G.: Modifications de l'électrocardiogramme après l'épreuve d'effort; leur intérêt dans les troubles de la circulation coronaire, Helvet. med. acta **3**: 652, 1936.

13. Puddu, V.: Alterazioni elettrocardiografiche da sforzo, in sogetti normali e anginosi, con particolare riguardo alla derivazione toracica, Cardiologia **2**: 183, 1938.

14. Cooper, E. L., O'Sullivan, J., and Hughes, E.: Athletics and the heart: an electrocardiographic and radiological study of the response of the healthy and diseased heart to exercise, M. J. Australia **24**: 569, 1937.

15. Rosenberger, I.: Ueber Arbeitsversuche und Elektrokardiogramm, Wien. klin. Wchnschr. **47**: 648, 1934.

16. Sensenbach, W.: Some common conditions, not due to primary heart disease, that may be associated with changes in the electrocardiogram, Ann. Int. Med. **25**: 632, 1946.

17. Hellebrandt, F. A., and Karpovich, P. V.: Fitness, fatigue and recuperation. Survey of methods used for improving the physical performance of man, War Med. **1**: 745, 1941.

18. Mainzer, F., and Krause, M.: The influence of fear in the electrocardiogram, Brit. Heart J. **2**: 221, 1940.

19. Stein, I.: Abnormal T-waves in patients presenting no evidence of organic heart disease, J. Lab. and Clin. Med. **31**: 837, 1946.

20. Walser, A.: Über den Einfluss vegetativer Pharmaka auf den Ablauf der T-Zacken-Veränderungen im Arbeits-Elektrokardiogramm, Cardiologia **10**: 231, 1946.

21. Baum, W. S., Malmo, R. B., and Sievers, R. F.: A comparative study of the effects of exercise and anoxia upon the human electrocardiogram, J. Aviation Med. **16**: 422, 1945.

22. Battro, A., and Araya, E.: Importancia de las derivaciones precordiales en el electrocardiograma de esfuerzo do la angina de pecho. Accion de ciertas drogas (trinitrina, aminofilina y papaverina), Medicina, Buenos Aires **7**: 101, 1947.

23. Donovan, M. A.: Pain of unusual duration due to progressive coronary occlusion with associated mediastinal tumor, Am. Heart J. **32**: 786, 1946.

24. Greene, C. W., and Gilbert, N. C.: Studies on the response of the circulation to low oxygen tension: changes in the pacemaker and in conduction during extreme oxygen want as shown in the human electrocardiogram, Arch. Int. Med. **27**: 517, 1921.

25. Rothschild, M. A., and Kissin, M.: Induced general anoxemia causing S-T deviation in the electrocardiogram, Am. Heart J. **8**: 745, 1933.
26. Katz, L. N., Hamburger, W. W., and Schutz, W. J.: The effect of generalized anoxemia on the electrocardiogram of normal subjects. Its bearing on the mechanism of attacks of angina pectoris, Am. Heart J. **9**: 771, 1934.
27. Levy, R. L., Williams, N. E., Bruenn, H. G., and Carr, H. A.: The "anoxemia test" in the diagnosis of coronary insufficiency, Am. Heart J. **21**: 634, 1941.
28. Wilson, F. N., Rosenbaum, F. F., and Johnson, F. W.: Interpretation of the ventricular complex of the electrocardiogram, *In:* Advances in Internal Medicine, New York, Interscience Publishers, 1947, Vol. II, p. 1.
29. Twiss, A., and Sokolow, M.: Angina pectoris—significant electrocardiographic changes following exercise, Am. Heart J. **23**: 498, 1942.
30. Barker, P. S., Shrader, E. L., and Ronzoni, E.: The effects of alkalosis and of acidosis upon the human electrocardiogram, Am. Heart J. **17**: 169, 1939.
31. Ungerleider, H. E., Duhigg, T. F., and Gubner, R. S.: Examination of the heart in Navy applicants, U. S. Nav. M. Bull. **41**: 441, 1943.
32. Wolf, G. A., Jr., and Wolff, H. G.: Studies on the nature of certain symptoms associated with cardiovascular disorders, Psychosom. Med. **8**: 293, 1946.
33. Heyer, H. E., Winans, H. M., and Plessinger, V. I.: Alterations in the form of the electrocardiogram in patients with mental disease, Am. J. M. Sc. **214**: 23, 1947.
34. Wolf, S.: Sustained contraction of the diaphragm, the mechanism of a common type of dyspnea and precordial pain. Proc. 39th Ann. Meet. Am. Soc. Clin. Invest., p. 35, May 5, 1947; also J. Clin. Invest. **26**: 1201, 1947.
35. Biörck, G.: Ergotamine and apparent coronary insufficiency, Brit. Heart J. **9**: 181, 1947.
36. Berk, L. H.: Cardiovascular syphilis. A clinical and electrocardiographic study, New York State J. Med. **41**: 223, 1941.
37. Gore, I., and Saphir, O.: Myocarditis, a classification of 1402 cases, Am. Heart J. **34**: 827, 1947.
38. Proger, S., and Dekaneas, D.: Some effects of injected cytochrome C in myocardial and cerebral anoxia in man, J. Pediat. **29**: 729, 1946.
39. Dack, S., Stone, J., Grishman, A., and Master, A. M.: Differential diagnosis of diaphragmatic hernia and coronary heart disease, Bull. New York Acad. Med. **24**: 396, 1948.
40. Master, A. M., Dack, S., and Jaffe, H. L.: Cardiac efficiency and prognosis following recovery from acute coronary occlusion. The results of various functional tests, J. A. M. A. **120**: 1271, 1942.
41. Biörck, G.: Anoxemia and exercise tests in the diagnosis of coronary disease, Am. Heart J. **32**: 689, 1946.
42. Alzamora Castro, V.: Contribución al conocimiento del significado de las modificaciones del segmento ST y de las ondas T, Gac. med. Lima **2**: 287, 1946.
43. Graybiel, A.: A consideration of the effects of oxygen lack of the cardiovascular system from the viewpoint of aviation. With an analysis of death occurring aloft on commercial aircraft, J. Aviation Med. **12**: 183, 1941.
44. Benson, O. O., Jr.: Coronary artery disease. Report of fatal cardiac attack in a pilot while flying, J. Aviation Med. **8**: 81, 1937.
45. Master, A. M., Dack, S., Grishman, A., Field, L. E., and Horn, H.: Acute coronary insufficiency: an entity. Shock hemorrhage and pulmonary embolism as factors in its production, J. Mt. Sinai Hosp. **14**: 8, 1947.
46. Dietrich, S., and Schwiegk, H.: Das Schmerzproblem der Angina pectoris, Klin. Wchnschr. **12**: 135, 1933.
47. Holzmann, M., and Wuhrmann, F.: Der Arbeitsversuch im Elektrokardiogramm, Deutsche med. Wchnschr. **62**: 685, 1936.
48. Burnett, C. T., Nims, G. M., and Josephson, C. J.: The induced anoxemia test; a study by age groups, Am. Heart J. **23**: 306, 1942.
49. Ruskin, A.: Pitressin test of coronary insufficiency, Am. Heart J. **34**: 569, 1947.

BLOOD DYSCRASIAS SECONDARY TO GOLD: WITH A CASE OF HYPOPLASTIC ANEMIA CURED BY SPLENECTOMY *

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Hematologic reactions are among the rarer, but more serious results of chrysotherapy; of these thrombocytopenia is by far the commonest. Granulocytopenia and aplastic anemia have been reported less frequently. Of the three dyscrasias aplastic anemia has proved most fatal.

Thrombocytopenia. More cases of hemorrhagic purpura than of any other blood disorder have been recorded following gold administration. It is remarkable that in many reports platelet counts are not given, and so thrombocytopenia, in some cases, can only be assumed.

Emile-Weil [1] reported one case of hemorrhagic purpura in 1931; he and Bousser [2] later referred to 30 instances of "hemorrhagic accidents," but the exact nature of these reactions was not indicated. In 1939 Wintrobe [3] was able to collect only seven cases [4, 7, 8, 9, 10] among whom there were three reported recoveries. Hartfall had, however, by 1937 already reported nine cases with six recoveries.[4, 5, 6] Ellman and Lawrence [11] in 1938 recorded one fatal case which was, however, associated with agranulocytosis. Snyder [12] in 1942 reported a further fatal case. Price and Leichtentritt [13] reported three cases of which one was fatal. Cecil et al.[14] also reported three hemorrhagic purpuras, all of whom recovered. Recently Mettier and his associates [15] have reported four further non-fatal cases of thrombocytopenic purpura following chrysotherapy.

Granulocytopenia. Wintrobe [3] collected 10 cases of this dyscrasia following gold therapy,[4, 16, 17, 18, 19, 20, 21, 22] eight of whom recovered. Since 1939 a number of further cases have been observed.[14, 23, 24, 25, 26, 27]

Aplastic Anemia. Apparently only 19 adequately documented cases of aplastic or hypoplastic anemia following gold therapy have been reported. Many other cases have undoubtedly been observed and either not reported or cited too casually to warrant inclusion in a review.

Dameshek [16] collected five cases [28, 29, 30, 31] in 1934 to which he added one of his own. Wintrobe [3] in 1939 collected a further six [32, 33, 34, 35, 36, 37] to which he also added one. Six further cases [38, 39, 40, 41, 42] have been reported. The gravity of this dyscrasia is emphasized by the fact that recovery occurred in only five (or 26 per cent) of these 19 reported cases, while the remaining 14 (or 74 per cent) died. In Wintrobe's own case, which recovered, a persisting macrocytosis was observed; he had previously pointed out [43] that

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such macrocytosis may be associated with extramedullary hematopoiesis, and it is interesting to speculate how large a part this process may play in those cases which show spontaneous recovery.

The concept of hypersplenism has lately modified our attitude towards the pathogenesis and treatment of many blood dyscrasias. Considerable evidence has accumulated that the spleen exerts, both in health and disease, an inhibitory effect on the bone marrow. After its removal for a variety of conditions leukocytosis, thrombocytosis, and Howell-Jolly bodies are commonly found.[44] Nucleated red cells and reticulocytosis have also been described. Cellular hyperplasia of the marrow may follow splenectomy.[45] In dogs rendered anemic by bleeding or phenylhydrazine injections, the number of normoblasts and of primitive erythroblasts in the peripheral circulation is much greater in splenectomized animals than in those whose spleens have not been removed.[46]

Splenic hyperfunction has been accepted for some time as one of the operative mechanisms in congenital hemolytic jaundice and thrombocytopenic purpura; more recently "splenic neutropenia" [47] and "splenic panhematopenia," [48] in which hyperfunction of the spleen is regarded as the sole causative mechanism, have been described. The situation as generally accepted today [49] may be summarized thus: the spleen normally exerts definite effects on the bone marrow, causing both quantitative and qualitative changes in the blood cells; when these become abnormally pronounced the condition is termed hypersplenism, which may take any one of the following forms:

(a) Thrombocytopenia
    1. primary splenic (idiopathic thrombocytopenic purpura)
    2. symptomatic
(b) Neutropenia
    1. primary splenic
    2. symptomatic
(c) Anemia
    1. primary splenic (congenital hemolytic icterus)
    2. symptomatic
(d) Any combination of (a), (b) and (c).
(e) Pancytopenia
    1. primary splenic
    2. symptomatic

Thus in any of these reductions of circulating cells the underlying pathogenesis may be either a primary splenic hyperfunction, or an overactivity symptomatic of the splenomegaly produced by another disease process (for example, portal cirrhosis, Gaucher's disease, Felty's syndrome, splenic tuberculosis, etc.) In all cases the marrow is cellular.

There are several mechanisms whereby the spleen may exert its influence to reduce the numbers of circulating blood elements; these are

(a) within its own confines—sequestration, hemolysis and phagocytosis;
(b) by hormonal effect on the marrow—suppression of maturation and control of delivery into the circulation.

There is and has been much dispute whether hyperfunction of the spleen is mainly a locally destructive action or a distant hormonal effect.

From their studies on the life cycle of erythrocytes before and after splenectomy (in which they found the practically identical values of 113 and 105 days), Singer and Weicz [50] conclude that the spleen plays no part in physiological blood destruction, and that there is no evidence for the existence of a primary hemolytic hypersplenism. Hirschboeck,[51] however, in a case of Felty's syndrome, demonstrated a reduction in leukocyte concentration from 11,700 per cu. mm. in splenic arterial blood to 2,600 in splenic venous blood (taken from each vessel just before ligature in the course of splenectomy). Doan [52] has reported similar findings. Such findings, however, are not the universal experience. In a case of our own of congestive splenomegaly recently subjected to splenectomy, the splenic arterial blood contained 10,000 leukocytes per cu. mm., while the splenic venous blood revealed a count of 13,050; there was no significant difference in erythrocyte and platelet counts. Such observations as those of Hirschboeck, and of Doan, however, at least suggest that leukocytes are trapped by the spleen, and favor the locally destructive rather than the hormonal theory. Pathological studies, for the most part, also support this theory; von Haam and Awny [53] examined spleens from 134 cases of hypersplenism (including 45 cases of hemolytic icterus, 36 of thrombocytopenic purpura, 11 of splenic neutropenia, 10 of splenic pancytopenia, and 32 of secondary type); they found

(a) increase in reticulo-endothelial cells, with diffuse and nodular hyperplasia;
(b) sequestration of blood elements in pulp and sinusoids, involving specifically those elements which were missing from the peripheral blood;
(c) increased, though not excessive, cell destruction by phagocytosis.

They conclude that blood destruction in the hyperplastic spleen cannot be explained by the process of phagocytosis alone, and they postulate (with the promise of proof to follow) a humoral factor which exerts an hemolytic and cytolytic effect upon sequestered blood cells. Though most pathological descriptions agree in the main with their description of the spleen in hypersplenism, some authors have noted an absence of abnormal phagocytosis,[54, 55, 56, 57] and one, at least, an absence of reticulo-endothelial hyperplasia.[55]

Much further evidence also favors the hormonal theory—the hyperplasia and maturation arrest seen in marrow smears in cases of hypersplenism; the slow rise in circulating cells following splenectomy over a period of days or weeks, as would be anticipated in an escape from maturation arrest, rather

than the abrupt rise which would be expected after removal of an abnormally destructive spleen; the presence of old segmented granulocytes, and the absence of metamyelocytes and myelocytes in the circulating blood when leukopenia is present.

The hormonal theory is further supported by approach from another angle—experimental work with spleen extracts. In 1938 Troland and Lee [58, 59] found that acetone extracts of spleens from patients with idiopathic thrombocytopenic purpura produced a marked lowering of platelets when injected into rabbits; they therefore called the active principle of their extracts "thrombocytopen." Although some subsequent workers [60, 61] failed to confirm this, others [62, 63, 64] have since succeeded in demonstrating a platelet depressing substance. In 1944 Cronkite [65] reported further confirmatory work, and extended it to demonstrate an even more potent platelet-depressing factor; this extract was from the spleen of a patient who had malignant neutropenia with *thrombocytosis* rather than thrombopenia. He claims therefore that thrombocytopen is not, as was hitherto thought, a substance specific to the spleen of idiopathic purpura. Moolten [66] demonstrated in the following year that normal spleens contain thrombocytopen, while other tissues do not, and that the spleen in hemorrhagic purpura contains at least 10 times as much as the normal spleen.

It seems probable that the overactive spleen exerts its hemocytopenic effects by different mechanisms in different diseases, and sometimes by a combination of cell-destruction and marrow-suppression.

Thus, from our knowledge of the normal and abnormal activities of the spleen, it is rational at least to consider splenectomy in two types of cases in which there is a reduction in circulating myeloid elements:

(a) where frank splenic hyperfunction operates as the cause of the dyscrasia; in these cases the cytology of the cellular marrow is that of a functioning organ and indicates a better prognosis;

(b) where the marrow is unregenerative, but nevertheless, it is hoped that removal of the normal restraining action of the spleen upon the marrow will encourage a reluctant organ to resume function; here hope is slim and the prognosis correspondingly worse.

Splenectomy has been employed successfully in idiopathic thrombocytopenic purpura since 1916, and has now become established as its most effective treatment [67, 68]; this is too well recognized to warrant a review of pertinent reports. With secondary thrombocytopenia, however, the situation is different. According to Wintrobe [67] "splenectomy is never indicated unless the primary disorder itself warrants it." Elliott,[68] however, emphasizes that this is an erroneous belief; he cites four cases of his own in which splenectomy was performed for thrombocytopenic purpura following gold therapy. Two of these four showed complete arrest of the thrombocytopenia, and one derived marked benefit, while one was lost to follow-up. In eight other cases, where the thrombocytopenia was secondary to other diseases, results

were unsatisfactory except in one case of splenic tuberculosis. In one of Mettier's cases [15] the thrombocytopenia and hemorrhagic proclivity progressed to dangerous degrees; splenectomy was performed and followed by an immediate and lasting improvement. Thus there have been four reported cases of thrombocytopenia secondary to chrysotherapy which have responded favorably to splenectomy.

Splenectomy in conditions of neutropenia is now well recognized. It has been employed with success in Felty's syndrome since 1932.[69, 70, 71, 72, 73] Recently the operation has been performed with increasing frequency [74, 75, 47, 76, 54, 77, 55, 56, 78, 57, 73] in primary splenic neutropenia. All these cases had clinically enlarged spleens and were cured by splenectomy. Hattersley [79] reported a case of chronic neutropenia, which had some features suggestive of hypersplenism, but there was no splenomegaly and the neutropenia was not cured by splenectomy. It is not therefore considered as a case of *splenic* neutropenia.

There have been a number of cases of hypoplastic and aplastic anemia reported in which, as a desperate last resort, splenectomy has been tried. In 1931 Rosenthal [80] reported three cases in adults where splenectomy had no effect. Van Leeuwen [81] in 1933 reported one child with Fanconi's syndrome in which no benefit resulted. The following year Gottlieb [82] had one transient success in a 19 year old, but relapse and death followed after a brief and incomplete remission. Illing [83] in 1939 put on record one case in a child where death followed within 10 hours of operation. In 1941 Doan [84] reported the case of a woman who developed hypoplastic anemia from exposure to benzol, and who was completely cured by splenectomy; a second case, resulting from injudicious contact with poison sprays, was only partially benefited. These are the only reported cases we can find in which a secondary hypoplastic anemia has been treated with splenectomy. Shaw and Oliver [85] in 1945 reported the case of a man aged 54 who developed a "primary" aplastic anemia; his hemoglobin fell to 28 per cent, red blood cells to 900,000, and leukocytes to 1,800 (of which 53 per cent were polymorphs); the color index was 1.5; no platelet count before operation is mentioned. Following splenectomy the patient's blood count rose to normal, with platelets to 1,126,000, and remained so up to the time of the report five months later; platelets at this time were 435,000. Dacie and Gilpin [86] in the previous year reported a case of familial hypoplastic anemia of Fanconi type, in which a "definite and sustained improvement" followed operation. Another similar case was reported by Estren et al.[87] in 1947 with pronounced improvement; these authors conclude that the justification for performing splenectomy probably depends on the presence of (a) megakaryocytes in the bone marrow, and (b) reticulocytes in the blood. In this same vein Dameshek [88] states "to remove the spleen when the marrow megakaryocytes are greatly lacking, or altogether absent, is to invite disaster." Whitby and Britton [89] record six "fully investigated cases" in whom splenectomy was performed with an "extremely successful result." No further details are

given; they continue "we have also had complete failures, though none have been made worse." Wise and Phelan [90] mention two cases of "hypoplastic anemia," one congenital and the other acquired, on whom splenectomy was performed; no benefit followed in the congenital case, but excellent results attended the other. This latter case is the subject of the present report. In this case it was felt that the anemia at many times was insufficiently explained by hemorrhage; and the white count, even in the face of hemorrhage and infection, was definitely, though mildly, leukopenic. These features, together with the definite thrombocytopenia, warranted the designation of mild aplastic or hypoplastic anemia. We can find no other reported cases of hypoplastic or aplastic anemia secondary to gold in which splenectomy was performed.

Case Report

A white housewife aged 52 years, was admitted to hospital on June 22, 1947. Her chief complaint was a productive cough with purulent, sometimes bloodstained sputum, of three weeks' duration. She had also noted shortness of breath, and she stated that she had spat up blood repeatedly during the last three or four days. She had, on occasion, noticed swelling of her ankles. She had suffered no chest pain, no chills, and no loss of appetite, but she had lost about 10 pounds.

She stated that she had developed rheumatoid arthritis about 15 months previously, for which she had received intravenous therapy with typhoid vaccine in August 1946. Despite the fact that her arthritis had greatly improved following this treatment, she was subjected to eight gold injections over a period of three months, beginning in January 1947. She developed purpura, however, and was treated with BAL; she had three or four injections of this, to which she reacted febrilely and locally. She reported that the systemic reactions were so severe that she would not consider further therapy with this agent. She was also given three blood transfusions; to the last of these she had a violent reaction consisting of high fever, "stomach discomfort," fainting and fever blisters. She had also been taking "various medicines" for her anemia.

Her menses stopped in December 1946, but in April 1947 she again began to menstruate and continued for two weeks; in May she had further menorrhagia for one week. Three weeks before admission her blood had been reported on as follows: hemoglobin 75 per cent, red blood cells 3.65 million, white blood cells 5,600 (78 per cent polymorphs, 22 per cent lymphocytes), and platelets 75,000.

Seventeen years previously she had suffered her first attack of parotitis, and since then had had occasional mild attacks. Six weeks before admission she had received oral penicillin for the latest of these.

It may be of interest to note that the patient's mother had had polyarthritis, splenomegaly and leukopenia, and had been diagnosed as Felty's syndrome some years before. Her father, uncle, brother, two first cousins and son had also all suffered from arthritis or rheumatic fever.

On admission to hospital physical examination revealed a well nourished, middle-aged white woman in no respiratory distress. Her weight was 166 lbs., pulse 74, temperature 99.2°, respirations 20, and blood pressure 120 mm. Hg systolic and 70 diastolic. Signs of consolidation were found at the base of her left lung, and pus could be expressed from both ducts of Stensen. Petechiae were present on her legs and on the buccal mucous membrane. The rest of the examination was essentially negative, except for occasional premature beats and bilateral saphenous varices. There was no evidence of arthritis and her spleen was not felt.

Investigations on admission were as follows: urinalysis and Kahn test negative.

Blood count—hemoglobin 68 per cent, red blood cells 3.08 million (MCV 113, MCHC 30 per cent), white blood cells 3,550 (stab 6 per cent, segmented 51 per cent, lymphocytes 39 per cent, eosinophiles 4 per cent), platelets 80,320 (normal 500,000). Roentgen-ray of chest showed infiltration of the left lung base. Further blood studies showed normal sugar and urea; uric acid 4.5 mg.; serum albumin 3.5 g., globulin 4.1 g. (A/G ratio 0.8); van den Bergh 0.5 mg., icteric index 3.8; sedimentation rate (Wintrobe) 53 mm. in one hour, packed cells 34, corrected rate 30; prothrombin time 17 seconds with undiluted plasma, 112 seconds in 12½ per cent plasma; bleeding time 2 minutes 45 seconds, and coagulation time 17 minutes 30 seconds (normal 5–10 minutes); clot retraction—none in 24 hours. Cephalin flocculation test—four plus; bromsulfalein—less than 1 per cent retention in 45 minutes, no retention at 60 minutes. Göthlin index of capillary fragility was 10.

The patient remained in hospital for 22 days; her course was characterized by a low grade fever for the first two weeks, during which time her pneumonia slowly resolved. On July 1 there was no appreciable change in the appearance of the roentgenogram, but by July 10 there was "considerable resolution of the pneumonic process, with still some residual changes." She was treated at first with penicillin by intramuscular injections and by aerosol, and later with streptomycin. All sputa were negative for tuberculosis, but on July 8 a specimen obtained by postural drainage grew α-hemolytic streptococci and *B. coli* on culture.

During her stay in hospital she suffered from menorrhagia, and recurrent ecchymoses appeared on her legs and thighs. Further hematologic studies between June 27 and July 14 are shown in the table. Vitamin C determination on June 26 was 0.49 mg., and on July 2 0.83 mg. Prothrombin times on June 28 were 16 and 77 seconds. Serum proteins on July 9 were albumin 4.6 gm., globulin 2.6 gm. (A/G ratio 1.7). On July 5 sternal biopsy revealed a moderately cellular marrow; no abnormal cells, and no megakaryocytes were seen. On July 7 the patient received a blood transfusion of 250 c.c., which was followed by a severe reaction with chills. Because of this reaction, and the history of her previous reaction following transfusion before admission, her blood was sent to Dr. A. S. Wiener for investigation. He classified it as O MN Rh_1 Rh_1 Hr negative, and the donor's blood as O N Rh_1 rh Hr positive; there were no Rh antibodies in the patient's blood—this did not necessarily exclude the possibility of Hr sensitization since the patient was Hr negative and the donor Hr positive.

Other hematinic measures employed included folic acid 15 mg. intramuscularly daily for the first 16 days, and thereafter 5 mg. orally t.i.d. until discharge, liver diet and vitamins. BAL was not administered. The patient received x-ray therapy in four divided doses over each parotid gland.

On the whole she responded well; platelets and white cells reached almost to normal, and the anemia apparently was responding to iron. The patient insisted on going home, and was discharged on July 15 weighing 171.5 lbs. The final diagnosis was pneumonitis, bilateral suppurative parotitis and mild aplastic anemia secondary to gold therapy.

At home she continued to take iron, folic acid and vitamins. Although she developed numerous petechiae, and experienced many episodes of spontaneous subcutaneous bleeding, blood counts as an out-patient on July 28 and August 22 showed no significant change in her hematologic picture. She had experienced menorrhagia for the week beginning July 28, and her next period, which began on August 25, was again menorrhagic. From August 29 she noticed shortness of breath, increasing fatigability and tiredness, and on September 3 was readmitted to hospital with her period still in progress.

Her weight on admission was 173 lbs.; her blood pressure was 96/62, pulse 78, temperature 98.6°, and respirations 20. She presented marked pallor. Ecchymoses

were present at the right elbow, over her left upper arm, both legs and left lower quadrant of the abdomen. Her right pupil was noted to be larger than her left, but both reacted normally. A bloodstained, purulent, postnasal discharge was observed. Her lungs were clear, the spleen again not palpable, and the rest of the physical examination was unremarkable.

TABLE I

Blood Counts

Date	Hb %	RBC	WBC	Stab	Segm.	Lymph.	Mono.	Eos.	Bas.	Platelets	
June 2, 1947	71	3.65	5,600		78	22				75,000	
(1st admission)											
23	68	3.08	3,550	6	51	39		4		80,320	MCV 113 MCHC 30%
27	76	3.85	6,600							107,800	
July 1	68	3.35	7,000	6	66	28				167,500	
2	68	3.24	5,650	7	55	33	1	4			
7	49	2.17	5,150	10	64	26					
(Transfusion)											
8	60	3.20	5,150	6	52	39		3		262,000	
10	53	3.01	5,450	10	53	37				150,400	
12	65	3.21	6,350	10	65	25				224,700	
14	60	3.12	6,300		69	25		5		173,600	
(Discharged)											
28	69	3.19	5,300	3	73	20		4		191,400	
Aug. 22	69	3.42	5,200	14	54	25	2	1		109,440	
(2nd admission)											
Sept. 3	48	2.46	3,950	20	43	35		2		108,240	
(Transfusion)											
4	48	2.58	4,750	13	53	31	1	2			MCV 108 MCHC 27%
5	57	2.76	6,150	4	64	23	1	8		81,760	
(Transfusion)											
6	67	3.32	4,400	12	52	32	1	3		86,320	
8	76	3.66	4,750	4	60	26	9		1	95,160	
(Transfusion)											
10	68	3.48		8	65	19	4	3	1	97,440	
(Transfusion)											
12	74	3.42	6,750	12	59	23		6		102,600	
13	75	4.17	6,300	16	50	25	2	7		103,420	
15	60	3.41	5,500	15	60	18	1	6		120,580	
15	61	3.14	11,450	2	74	19	3	2			
(Transfusion)											
18	66	3.21	5,500	15	66	16	2	1		96,300	
20	61	3.14	5,000	16	58	21	1	4		100,480	
25	56	3.15	4,300	1	62	31		6		69,300	
(Transfusion)											
27	77	3.76	5,900		63	30	2	2		97,760	
(Splenectomy and two transfusions)											
29			14,850	6	76	16		2		96,600	
Oct. 1	63	3.31	14,400	13	65	19		3		112,540	
3	64	3.05	15,600	9	72	10	4	5		262,300	
6	57	3.05	7,300	4	63	21	4	8		292,800	
8	65	3.20	13,000	10	62	26		2		1,152,000	
9	68	3.11	10,000		76	19	2	3		1,076,060	
11	64	3.25	9,800	3	71	22	1	4		1,027,000	
13	66	3.50	9,200	8	59	27		6		867,000	
15	76	3.75	7,500	8	60	24	3	5		830,000	
16	76	3.70									MCV 97 MCHC 31%
17	77	3.95	8,600	9	55	30	4	2		985,400	Retic. 1.4%
(Discharged)											
Nov. 13	80	4.04	5,050	5	37	40	12	4	2	428,240	
Jan. 5, 1948	88	4.20	6,400	9	44	32	4	11		487,200	
Mar. 24	86	4.45	5,750	2	48	40	2	8		329,300	
Oct. 21	82	4.11	9,550	5	42	43	5	5		344,400	

A blood count on admission showed hemoglobin 48 per cent, red blood cells 2.46 million (MCV 108, MCHC 27 per cent), white blood cells 3,950 (stab 20 per cent, segmented 43 per cent, lymphocytes 35 per cent, eosinophiles 2 per cent), platelets 108,240; anisocytosis and poikilocytosis were marked. Bleeding time was 1 minute 35 seconds, and coagulation time 6 minutes 30 seconds. Sedimentation rate in one hour was 40 mm., packed cells 28, corrected rate 10. The following day the Göthlin index was 49, and an x-ray of the chest was reported on as follows: "quite a residual clouding of the left lower lung field, which may represent thickened pleura."

On the day of admission she was given about 450 c.c. of typed and matched blood, group O, Rh positive, Hr positive. After 50 c.c. had run in, a serum sample

from the patient was spectroscoped for hemoglobin; no hemolysis was detected. Completion of the transfusion was, however, followed by a severe febrile reaction with chills and temperature to 104°. Two days later she was given a second transfusion; the blood used was Rh positive Hr negative; she was given sodium phenobarbital grs. 3 by injection before the transfusion, and the same spectroscopic precaution was observed after 50 c.c. had been administered. No hemolysis was detected, and no reaction followed this transfusion. On September 9, as there was no available Hr negative blood, the patient received a transfusion of Hr positive blood; this was followed by a moderately severe febrile reaction. Similar reactions attended subsequent transfusions on September 11 and 17. On September 11 sternal marrow puncture showed a fairly normal differential, with 0.2 per cent megakaryocytes. Sternal biopsy on September 16 was reported on as follows: "Cross section of bone presents a normal cortex and bone septa, with intact osteoblasts. The medullary spaces are occupied by adipose tissue. The myelogenous element is hypoplastic; the cells are sparsely distributed; occasional islands of marrow appear essentially normal; myelocytes, megakaryocytes and nucleated reds are encountered. There is no fibrosis. Moderate hypoplasia." The range of blood counts between September 4 and 20 may be seen in the table. Blood chemistry, van den Bergh, icteric index, vitamin C blood level, plasma protein and prothrombin time were normal. Cephalin flocculation test was again four plus.

Besides the transfusions the patient was treated with folic acid, Feosol, vitamins, rutin, hesperidin and penicillin. She showed little or no response to conservative measures; her bleeding diathesis persistently manifested itself in subcutaneous hemorrhages, and her platelet count reached its lowest ebb (69,300) on September 25. Because of this and her obstinate intolerance of transfusions, with a measure of reassurance afforded by the presence of megakaryocytes in the marrow, it was decided to remove her spleen in the hope that she would be benefited. This decision was concurred in by Dr. Paul W. Clough in consultation. Accordingly, on September 29, splenectomy was performed by Dr. Daniel Pessagno. Omental adhesions were found round the spleen; these were freed without difficulty. The patient withstood the operation well. During the day she received a total of 1000 c.c. of whole blood without reaction. The pathological report on the spleen read as follows: "Average sized spleen, showing marked hypertrophy of the germinal follicles within the Malpighian bodies. There is a proliferation of cells which have the characteristics of myeloid tissue. Nucleated cells are numerous and occasional mononucleated cells are encountered. Zones surrounding the germinal follicles are composed of compact lymphocytes which form a very compact stroma. The sinusoids are engorged with histiocytes, most of which contain fine dust-like pigment. There is nothing to suggest neoplasm and no hemorrhage. Summary: splenomegaly, characterized by hypertrophy and hyperplasia of the germinal follicles within the Malpighian bodies."

The hematological response to operation was dramatic. Within four days her platelets numbered 262,300, and in 10 days the count was over a million. She received no transfusions after the day of operation. On October 18 she was discharged from hospital greatly improved clinically, and with 77 per cent hemoglobin, 3.95 million erythrocytes, 8,600 leukocytes and 985,400 platelets. She has now been followed for one year, and symptomatically and hematologically the improvement has been well maintained. Apart from a further mild attack of parotitis recently, she has been in excellent health. Her weight has returned to the level which she enjoyed five years ago (198 lbs.). She has had no further hemorrhages and no menorrhagia. No joint symptoms have returned. A blood count on October 21, 1948, showed hemoglobin 82 per cent, red blood cells 4.11 million, white blood cells 9,550, and platelets 344,400.

Discussion

It is not intended that this report should argue in favor of earlier and more frequent splenectomies in cases of hypoplastic or aplastic anemias following gold therapy. Conservative measures should be adopted first, and only when these have failed should we resort to splenectomy. Of such measures the use of BAL is perhaps the most promising. Fitzpatrick [42] reports its unsuccessful use in one case of aplastic anemia following gold therapy, in which the patient was alive hardly long enough to test its therapeutic efficacy. More recently Macleod [91] has reported a case of "hypoplastic" anemia following chrysotherapy in which BAL failed to improve blood or marrow picture. No blood counts are mentioned in this case, and BAL was not administered until 10 months after gold therapy; by which time, no doubt, the marrow changes had become irreversible. It has been used with success, however, in other blood dyscrasias following gold treatment: Lockie et al.[27] report "spectacular" recovery in one case each of thrombocytopenic purpura and granulocytopenia, and, of course, it has been favorably reported upon in blood dyscrasias following arsenotherapy.[92] Gendel [93] has recommended that large doses of folic acid for a prolonged period be given a trial in aplastic anemia; he reports three cases in whom a remission of varying degree was associated with such therapy. In view, however, of the almost uniformly negative results in the experience of others, the results in these cases were probably not attributable to folic acid.[94]

The present case is presented to emphasize that if, despite supportive, antidotal and hematinic measures the marrow remains unregenerative, splenectomy may be a life-saving and curative measure. It also suggests the possibility that, in such cases of secondary blood dyscrasias cured by splenectomy, the toxic effect of gold may not be a directly depressing effect on the marrow. It may rather be an action on the spleen, stimulating it to hormonal overactivity with consequent maturation arrest and retention of blood elements in the marrow. The experimental demonstration that colloidal gold particles, after injection, are phagocytosed in large amounts by reticulo-endothelium, especially in the liver and spleen [95, 96] perhaps lends support to this very tentative hypothesis.

Summary

1. Reported cases of blood dyscrasias following gold therapy are briefly reviewed.

2. Hypersplenism is discussed. Evidence is presented for and against (a) a locally destructive hyperfunction of the spleen, and (b) an hormonal influence on the bone marrow.

3. Indications for splenectomy in blood dyscrasias are considered. Reported cases of (a) secondary thrombocytopenia, (b) neutropenia, and (c) "primary" and secondary aplastic or hypoplastic anemias, in which splenectomy was performed, are briefly reviewed.

4. A case of hypoplastic anemia, secondary to gold therapy and cured by splenectomy, is reported.

BIBLIOGRAPHY

1. Weil, P. E.: Le grand purpura hémorragique d'origine aurique, Paris méd. **81**: 102, 1931.
2. Weil, P. E., and Bousser, J.: Les états hémorragiques post-auriques, Le Sang **6**: 825, 1932.
3. Wintrobe, M. M., Stowell, A., and Roll, R. M.: Report of a case of aplastic anemia following gold injections in which recovery occurred, Am. J. M. Sci. **197**: 698, 1939.
4. Hartfall, S. J., and Garland, H. G.: Gold treatment of rheumatoid arthritis, Lancet **2**: 8, 1935.
5. Hartfall, S. J., and Garland, H. G.: Further observations on gold treatment of rheumatoid arthritis, *ibid.* **1**: 1459, 1936.
6. Hartfall, S. J., Garland, H. G., and Goldie, W.: Gold treatment of arthritis: review of 900 cases, *ibid.* **2**: 838, 1937.
7. Hudson, E. H.: Purpura haemorrhagica caused by gold and arsenical compounds, with report of two cases, *ibid.* **2**: 74, 1935.
8. Jones, H. W., Tocantins, L. M., and Corson, E. F.: Purpura hemorrhagica; intravenous gold as etiologic factor, Penn. M. J. **37**: 809, 1934.
9. Bruins Slot, W., and Winkler, K. C.: Purpura hemorrhagica following gold therapy, Nederl. tijdschr. v. geneesk. **80**: 232, 1936.
10. Urgoiti, A., and Hermida, J.: Sindrome hematico maligno mortal producido por la crisoterapia, Arch. d. med. cir. y. especialid. **38**: 117, 1935.
11. Ellman, P., and Lawrence, J. S.: Gold therapy in rheumatoid arthritis, Post-grad. M. J. **14**: 275, 1938.
12. Snyder, R. G., Traeger, C. H., and Squires, W. H.: Toxic reactions and death following gold therapy in chronic arthritis, Indust. Med. **11**: 425, 1942.
13. Price, A. E., and Leichtentritt, B.: Gold therapy in rheumatoid arthritis, Ann. Int. Med. **19**: 70, 1943.
14. Cecil, R. L., Kammerer, W. H., and dePhume, F. J.: Gold salts in treatment of rheumatoid arthritis: study of 245 cases, *ibid.* **16**: 811, 1942.
15. Mettier, S. R., McBride, A., and Li, J.: Thrombocytopenic purpura complicating gold therapy for rheumatoid arthritis, Blood **3**: 1105, 1948.
16. Dameshek, W.: Aplastic anemia following treatment of lupus erythematosus with gold sodium thiosulphate, New Eng. J. Med. **210**: 687, 1934.
17. Braillon, J.: Leucocytose pseudoleucémique après aurothérapie, Le Sang **8**: 99, 1934.
18. Chabaud, J., Ginsbourg, B., and Langlet, L.: Un cas de syndrome agranulocytaire aurique fruste, Bull. et mém. Soc. méd. d. hôp. de Paris **49**: 1238, 1933.
19. Hedfeldt, A.: Three cases of granulocytopenia in course of gold therapy, Nord. med. tidskr. **11**: 874, 1936.
20. Margarot, J., Plagniol, A., and Balmes, J.: "Xeroderma pigmentosum" avec coproporphyrinurie chez un sujet atteint de tuberculose osseuse et soumis à un traitement héliothérapique prolongé, Bull. Soc. franc. de derm. et syph. (réunion dermat.) **41**: 539, 1934.
21. Rheinheimer, E. W., and Smith, L. M.: Granulopenia, report of case following injection of gold and sodium thiosulphate, Southwest. Med. **17**: 239, 1933.
22. Wechsler, L.: Ein Fall von Agranulozytose durch Lopion, Wien. klin. Wchnschr. **50**: 1360, 1937.
23. Mirick, G. S.: Total agranulocytosis following gold therapy: report of case with recovery and review of literature, Am. Rev. Tuberc. **41**: 344, 1940.
24. Alvarez, A. C., and Ortega, J. A.: Granulocytopenia following gold therapy of pulmonary tuberculosis; case, Semana med. españ. **4**: 178, 1941.
25. Baleztena, M. M. E.: Agranulocytosis secondary to sodium gold thiosulfate therapy of pulmonary tuberculosis; case, Prensa med. argent. **31**: 85, 1944.

26. Boland, E. W., Headley, N. E., and Hench, P. S.: Treatment of agranulocytosis with penicillin: case resulting from chrysotherapy for rheumatoid arthritis, J. A. M. A. **130**: 556, 1946.
27. Lockie, L. M., Norcross, B. M., and George, C. W.: Treatment of two reactions due to gold; response of thrombopenic purpura and granulocytopenia to BAL therapy, *ibid.* **133**: 754, 1947.
28. Jacquelin, A., and Allanic, A.: Sur un nouveau cas d'agranulocytose post-chrysothérapique, Bull. et mém. Soc. méd. de hôp. de Paris, **48**: 539, 1932.
29. Achard, C., Coste, F., and Cahen, R.: A propos des désordres hématologiques provoqués par les sels d'or, *ibid.* **48**: 547, 1932.
30. Laignel-Levastine, A. F., and Reyt: Accidents hémorragiques au cours de la chrysothérapie, Le Sang **6**: 452, 1932.
31. Angeras and Ginsbourg: Aleucie hémorragique (agranulocytose) post-chrysothérapique, *ibid.* **6**: 798, 1932.
32. Jullien, W.: Aleucie hémorragique observée au cours d'un traitement par la crisalbine, Bull. et mém. Soc. méd. de hôp. de Paris **50**: 174, 1934.
33. Weissenbach, R. J., Martineau, J., Brocard, J., and Malinsky, A.: Anémie grave avec neutropenie et syndrome hémorragique après chrysothérapie, *ibid.* **52**: 1071, 1936.
34. Ellman, P., and Lawrence, J. S.: Agranulocytosis with purpura hemorrhagica following gold therapy, with note on prevention of complications, Brit. M. J. **2**: 622, 1935.
35. Gautier, C., Seidmann, P., and Baudouin, A.: Aleucie hémorragique avec anémie grave au cours de la chrysothérapie, Bull. et mém. Soc. méd. de hôp. de Paris **24**: 1194, 1936.
36. Lavergne, V. de, and Bichat, J.: L'aleucie hémorragique accident de la chrysothérapie, Rev. méd. de l'est. **63**: 457, 1935.
37. Weil, M. P., Oumansky, V., and Langlois, L.: Anémie aplastique hémorragique consecutive à la chrysothérapie, Ann. méd. **44**: 78, 1938.
38. Giraud, G., and Desmonts, T.: Effect of bone marrow administration in course of hypoplastic anemia following treatment with gold, Montpellier méd. **19**: 447, 1941.
39. Pergola, A.: Severe agranulocytic aleukia hemorrhagica following treatment with gold, Sang **16**: 37, 1944.
40. Armas Cruz, R., et al.: Panmieloptisis secundaria a sales de oro, Rev. méd. de Chile **68**: 1153, 1940.
41. Aubert, A.: Panmyelopathy (panmyelophthisis), Acta med. Scandinav. **123**: 377, 1946.
42. Fitzpatrick, W. J., and Schwartz, S. O.: Aplastic anemia secondary to gold therapy, Blood **3**: 192, 1948.
43. Wintrobe, M. M.: Relation of disease of liver to anemia; type of anemia, response to treatment, and relation of type of anemia to histopathologic changes in liver, spleen, and bone marrow, Arch. Int. Med. **57**: 289, 1936.
44. Singer, K., Miller, E. B., and Dameshek, W.: Hematologic changes following splenectomy in man with particular reference to target cells, hemolytic index and lysolecithin, Am. J. M. Sc. **202**: 171, 1941.
45. Krumbhaar, E. B.: Changes produced in blood picture by removal of normal mammalian spleen, *ibid.* **184**: 215, 1932.
46. Cruz, W. O., and Robscheit-Robbins, F. S.: Relationship between spleen and morphologic picture of blood regeneration, *ibid.* **203**: 28, 1942.
47. Wiseman, B. K., and Doan, C. A.: A newly recognized granulopenic syndrome caused by excessive splenic leucolysis and successfully treated by splenectomy, J. Clin. Investigation **18**: 473, 1939.
48. Doan, C. A., and Wright, C.-S.: Primary congenital and secondary acquired splenic panhematopenia, Blood **1**: 10, 1946.
49. Dameshek, W.: Medical progress: hematology, New Eng. J. Med. **234**: 829, 1946.
50. Singer, K., and Weicz, L.: Life cycle of erythrocyte after splenectomy and problems of splenic hemolysis and target cell formation, Am. J. M. Sc. **210**: 301, 1945.

51. Hirschboeck, J. S.: Hematologic effects of splenectomy in Still-Chauffard-Felty syndrome; report of two cases, Blood **1**: 247, 1946.
52. Doan, C. A.: Primary splenic panhematopenia, J. Lab. and Clin. Med. **30**: 385, 1945.
53. von Haam, E., and Awny, A. J.: The pathology of hypersplenism, Am. J. Clin. Path. **18**: 313, 1948.
54. Muether, R. O., Moore, L. T., Stewart, J. W., and Broun, G. O.: Chronic granulocytopenia caused by excessive splenic lysis of granulocytes: report of a case, J. A. M. A. **116**: 2255, 1941.
55. Rogers, H. M., and Hall, B. E.: Primary splenic neutropenia, Arch. Int. Med. **75**: 192, 1945.
56. Salzer, M., Ransohoff, J. L., and Blatt, H.: Primary splenic neutropenia with report of case, Ann. Int. Med. **22**: 271, 1945.
57. Semple, R.: Idiopathic hypersplenism; report of a case, Brit. M. J. **2**: 72, 1948.
58. Troland, C. E., and Lee, F. C.: Preliminary report on platelet-reducing substance in spleen of thrombocytopenic purpura, Bull. Johns Hopkins Hosp. **62**: 85, 1938.
59. Troland, C. E., and Lee, F. C.: Thrombocytopen: substance in extract from spleen of patients with idiopathic thrombocytopenic purpura that reduces number of blood platelets, J. A. M. A. **111**: 221, 1939.
60. Pohle, F. J., and Meyer, O. O.: Inability to demonstrate platelet reducing substance in acetone extract of spleen from patients with idiopathic thrombocytopenic purpura, J. Clin. Investigation **18**: 537, 1939.
61. Tocantins, L. M.: No platelet-destroying action in extracts of spleen and urine of patients with chronic thrombopenic purpura, Proc. Soc. Exper. Biol. and Med. **42**: 485, 1939.
62. Rose, H., and Boyer, L. B.: Thrombocytopen: confirmatory report, J. Clin. Investigation **20**: 81, 1941.
63. Paul, J. T.: Effect of splenic extracts from cases of essential thrombocytopenic purpura on platelets and hematopoietic organs of rabbits, J. Lab. and Clin. Med. **27**: 754, 1942.
64. Hobson, J. C. G., and Witts, L. J.: Platelet-reducing extracts of spleen, Brit. M. J. **1**: 50, 1940.
65. Cronkite, E. P.: Further studies of platelet-reducing substances in splenic extracts, Ann. Int. Med. **20**: 52, 1944.
66. Moolten, S. E.: Studies on extractable factors in spleen and other organic sources which influence blood platelet count, J. Mt. Sinai Hosp. **12**: 866, 1945.
67. Wintrobe, M. M.: Clinical hematology, 1946, Lea and Febiger, p. 622–24.
68. Elliott, R. H. E.: Re-evaluation of splenectomy in thrombocytopenic purpura, based on 27 year combined clinic follow-up experience (Lewis Linn McArthur lecture), Proc. Inst. Med. Chicago, **16**: 330, 1947.
69. Hanrahan, E. M., and Miller, S. R.: Effect of splenectomy in Felty's syndrome, J. A. M. A. **99**: 1247, 1932.
70. Craven, E. B., Jr.: Splenectomy in chronic arthritis associated with splenomegaly and leucopenia (Felty's syndrome), *ibid.* **102**: 823, 1934.
71. Steinberg, C. L.: The value of splenectomy in Felty's syndrome, Ann. Int. Med. **17**: 26, 1942.
72. Smith, S., and McCabe, E. S.: Primary splenic neutropenia with arthritis (so-called Felty's syndrome). Its treatment by splenectomy, *ibid.* **29**: 445, 1948.
73. Holland, C. W.: Splenectomy in hematological disorders, Canad. M. A. J. **59**: 13, 1948.
74. Nordenson, N. G., and Roden, S.: Chronic malignant granulocytopenia treated with splenectomy; recovery, Acta chir. Scandinav. **84**: 518, 1914.
75. Reissman, K.: Chronisch agranulocytäre Myelopathie als Folge splenopathischer Markhemmung, Med. Welt **12**: 16, 1938.
76. Moore, C. V., and Bierbaum, O. S.: Chronic neutropenia treated by splenectomy, New Internat. Clin. **3**: 86, 1939.

77. Wiseman, B. K., and Doan, C. A.: Primary splenic neutropenia; newly recognized syndrome, closely related to congenital hemolytic icterus and essential thrombocytopenic purpura, Ann. Int. Med. **16**: 1097, 1942.
78. Langston, W., White, O. A., and Ashley, J. D., Jr.: Splenic neutropenia; report of case with splenectomy, *ibid.* **23**: 667, 1945.
79. Hattersley, P. G.: Chronic neutropenia, Blood **2**: 227, 1947.
80. Rosenthal, N.: Hematological aspects of agranulocytosis and other diseases accompanied by extreme leukopenia, Am. J. Clin. Path. **1**: 7, 1931.
81. Van Leeuwen, H. C.: Ein Fall von "konstitutioneller infantiler perniziosaahnlicher Anamie" (Fanconi), Folia haemat. **49**: 434, 1933.
82. Gottlieb, R.: Myeloid insufficiency, Ann. Int. Med. **7**: 895, 1934.
83. Illing, T.: Beitrag zum Krankheitsbild der Panmyelophthise im Kindesalter, Folia haemat. **62**: 369, 1939.
84. Doan, C. A.: The differential diagnosis and treatment of those non-hemolytic anemic states failing to respond to adequate liver or iron therapy, J. Missouri State M. A. **38**: 393, 1941.
85. Shaw, M., and Oliver, L. C.: Aplastic anaemia treated by splenectomy, Proc. Roy. Soc. Med. **38**: 479, 1945.
86. Dacie, J. V., and Gilpin, A.: Refractory anemia (Fanconi type); its incidence in three members of one family, Arch. Dis. Childhood, **19**: 155, 1944.
87. Estren, S., and Dameshek, W.: Familial hypoplastic anemia of childhood; report of 8 cases in two families with beneficial effect of splenectomy in one case, Am. J. Dis. Child. **73**: 671, 1947.
88. Dameshek, W.: Editorial: marrow bone technics, Blood **3**: 209, 1948.
89. Whitby, L. E. H., and Britton, C. J. C.: Disorders of the blood, ed. 5, 1946, The Blakiston Co., Philadelphia, p. 384.
90. Wise, W. D., and Phelan, P. C.: A review of surgery of the spleen, South. M. J. **41**: 170, 1948.
91. Macleod, J. G.: BAL in the treatment of gold toxicity, Ann. Rheum. Dis. **7**: 143, 1948.
92. Holley, H. L.: The use of BAL (2,3-dimercaptopropanol) in the treatment of agranulocytosis following intensive arsenotherapy for syphilis, Ann. Int. Med. **27**: 231, 1947.
93. Gendel, B. R.: Folic acid in treatment of aplastic anemia, J. Lab. and Clin. Med. **32**: 139, 1947.
94. Editors, Year Book of General Medicine, 1947, Year Book Publishers, Chicago, p. 406.
95. Freyburg, R. H., Block, W. D., and Wells, G. S.: Gold therapy for rheumatoid arthritis; considerations based upon studies of metabolism of gold, Clinics **1**: 537, 1942.
96. Sabin, A. B.: New gold salt for treatment of rheumatoid arthritis; experimental and clinical studies, Proc. Staff Meet., Mayo Clin. **17**: 542, 1942.

THE CLINICAL AND METABOLIC EFFECTS OF PROGESTERONE AND ANHYDROHYDROXY-PROGESTERONE IN RHEUMATOID ARTHRITIS *

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DESPITE Hench's observation in 1933 [1] that improvement of the joint symptoms in rheumatoid arthritis commonly followed the occurrence of jaundice, practical application of this information met with but meager success.[2, 3, 4] Five years later, Hench added the significant observation that temporary remission of symptoms occurred frequently during pregnancy.[5] Until recently, this information, although repeatedly confirmed and thoroughly discussed, did little to advance the therapy of rheumatoid arthritis. Barsi [6] claimed effectiveness for transfusions of blood of pregnant women but it is the consensus at the present time that this form of therapy has little value.[7] Although a temporary remission of the symptoms of arthritis may occur following many traumatic stimuli, which, according to Hughes, diminish systemic resistance,[8] that seen with jaundice and pregnancy has been especially pronounced. The improvement associated with the latter state is more spectacular and consequently there has been great interest in attempting to determine which of the metabolic alterations of pregnancy is operative, and sequentially, if such a change could also be present in the patient with hepatitis.

Most prominent among the many metabolic changes during pregnancy is the marked increase in secretion of hormones, namely estrin, chorionic gonadotropin and progesterone. Study of the excretion of estrin and gonadotropin in female arthritic patients has revealed no significant variations.[9] Treatment with estrogenic material has not proved to be of any value in arthritis, except perhaps in that rare patient whose symptoms have been aggravated by a true menopausal state; and the administration of chorionic gonadotropin has proved equally ineffective.[10, 11] Progesterone, secreted by the ovary through gonadotropic stimulation early in pregnancy and later in much greater amounts by the placenta, has been given little trial in the treatment of rheumatoid arthritis. In fact, discussions of hormonal changes in pregnancy with reference to arthritis, have overlooked the increase in progesterone.[12] The only reported study that we could find was

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that of Touw and Kuipers,[13] who treated three arthritic patients, each of whom gave a history of remission of symptoms during pregnancy, with rather small doses of progesterone during the latter half of the menstrual cycle. In two of the patients temporary relief occurred after one course of injections and permanent improvement was said to have followed subsequent courses of therapy. The third patient experienced very little benefit.

Also of possible significance is the relation of hepatic function to progesterone metabolism. There is considerable evidence to suggest that the inactivation of progesterone is dependent upon normal liver function.[14] It has also been shown that the bile is one of the channels of egress from the body of derivatives of progesterone.[15] Consequently, an elevation of circulating progesterone might be expected to occur in jaundice especially when the latter is due to the obstructive phase of infectious hepatitis.

This study was predicated on the basis that increased blood levels of progesterone might be the factor responsible for the remission of symptoms in patients with rheumatoid arthritis, not only in pregnancy but also in hepatitis and jaundice. Our results are essentially negative. After the major portion of this investigation had been completed, the entire subject of arthritic therapy was dramatically stimulated by the studies of Hench, Kendall and their co-workers on the effect of Compound E (17-hydroxy, 11-dehydro corticosterone) (cortisone) in patients with arthritis.[16] Because progesterone has some actions common to other adrenal steroids and because the limited supply of these steroids will lead to trial of all similar compounds, this negative report is offered.

Plan of Study: As far as the number of patients under investigation would permit, cases were selected to allow adequate distribution with respect to age, sex, severity of joint involvement and chronicity of the disease. All the patients had typical features of rheumatoid arthritis and were studied during an active phase of the disease. The greater number were hospitalized on the metabolic ward; a few were followed in the out-patient clinic. Progesterone (Lutocylin *) was given by intramuscular injection to the majority of the patients, while those treated as out-patients were given anhydrohydroxyprogesterone (Lutocylol *) by mouth. Both drugs were used in four of the patients. The dose was calculated on the basis of the amount of pregnandiol excreted in the urine at the time of pregnancy when remission of arthritic symptoms is most prone to occur, i.e., after the third month, at which time 15 to 20 mg. of pregnandiol is excreted daily. Although this substance is equivalent to progesterone, molecule for molecule, at least 50 per cent is believed to be lost in the extraction process. Consequently, 40 mg. of progesterone were deemed necessary and a dose of 50 mg. was chosen as that which would give a margin of safety in equalling normal physiologic levels of circulating hormone during pregnancy. Inasmuch as Hamblen [17] found that less than 50 per cent of administered progesterone is recovered

* Kindly supplied by Dr. Houghton of the Ciba Pharmaceutical Company.

as pregnandiol, a number of patients were given 100 mg. of progesterone daily. Because of the knowledge that the effect of injected progesterone is short in duration, therapy was administered at least daily and usually in two daily doses. On the assumption that anhydrohydroxyprogesterone is at best one-fifth as potent as the intramuscular preparation, 200 mg. was chosen as the minimal daily dose necessary to achieve any therapeutic effect. Following the report by Hench and Kendall relative to the successful use of cortisone in the treatment of arthritis, two patients were treated with larger doses of progesterone by injection, i.e., 150 and 200 mg. a day, respectively.

All of the patients were followed for a control period prior to the institution of treatment. The clinical severity of their disease was measured in respect to pain, stiffness, swelling and limitation of motion, quantitation of these symptoms being recorded by two observers as well as the patient. Similar clinical evaluation was conducted throughout the period of therapy and for varying lengths of time thereafter. Several patients were followed carefully by the physical therapy department with measurement of active and passive movement of the affected joints before, during and after therapy. Administration of an inert placebo was conducted in those patients who showed definite clinical improvement while on progesterone with relapse after the withdrawal of medication.

Routine laboratory studies including hemograms, urinalyses and determination of sedimentation rates by the Wintrobe tube method were performed on all patients. The majority also had serial total eosinophile counts, measurement of lymphocyte percentage, cholesterol partition and serum calcium, phosphorus and alkaline phosphatase determinations. Studies of nitrogen balance, urinary calcium excretion, daily output of total neutral 17-ketosteroids, and creatine and creatinine excretion were made on a number of the hospitalized patients. Certain other studies including blood glucose and amylase levels were made in selected cases. The laboratory findings which are believed pertinent to this investigation are included below.

Case Reports

Case 1. A 44 year old white male with peripheral rheumatoid arthritis of six years' duration had experienced numerous acute episodes with redness, swelling and progressive deformity, and his disease had been increasing in severity for the year prior to hospitalization. Previous therapy had included intravenous typhoid vaccine, intravenous novocaine, numerous transfusions and gold. He was hospitalized on the metabolic ward and after a control period of eight days was given 50 mg. of intramuscular progesterone daily. During and following this treatment he showed no improvement and the sedimentation rate, which was moderately elevated, showed some increase during therapy.

Case 2. A 39 year old white male had rheumatoid arthritis and rheumatoid spondylitis of two and one-half years' duration. Initially, the peripheral joints were actively inflamed and reddened, but at the time of study there was chronic deformity with only moderate acute inflammatory reaction. He had previously received the usual types of therapy including x-ray to the spine and chrysotherapy for the

peripheral joints. For six months prior to hospitalization, his condition had been steadily deteriorating. After a control period of eight days he was given 50 mg. of progesterone intramuscularly daily for 20 days. There was no appreciable clinical improvement. His sedimentation rate was moderately elevated, and although there was a drop to within normal limits in the early phase of treatment, the rate had returned to the control level before therapy was concluded.

Case 3. A 41 year old white female with peripheral rheumatoid arthritis of approximately 10 years' duration had been going steadily downward for several months prior to treatment and showed both acute inflammatory reaction and chronic deformities of various joints. She had received routine therapy including gold without effect. Fifty mg. of progesterone were given daily for 22 days, followed by the oral preparation of anhydrohydroxyprogesterone, 150 mg. daily, for one week. Although there was some increase in motion of the arms, the symptoms of acute inflammation became more severe. The sedimentation rate was very high and remained elevated throughout her course. She was again seen one month after the completion of therapy at which time there was no change, and for the past year her condition has steadily progressed in severity.

Case 4. A 37 year old colored female with progressive rheumatoid arthritis of two years' duration had manifested continuous rheumatic activity with limitation of motion, pain and moderate swelling, involving particularly the elbows and fingers, throughout this two year period. The administration of progesterone, 50 mg. daily for 25 days, resulted in marked clinical improvement but there was no appreciable change in the definitely elevated sedimentation rate and no more than slight measurable increase in motion of the affected joints. Within one week after discontinuation of treatment, mild symptoms recurred and within one month these had increased to the degree of original severity. Three months after the termination of the first course of therapy, at which time the symptoms had become markedly increased in severity, she was treated in the out-patient department with 200 mg. of anhydrohydroxyprogesterone daily for 25 days. A marked clinical response ensued which has been maintained for the past nine months, preventing the administration of placebo medication. The sedimentation rate has remained markedly elevated throughout this period of time.

Case 5. A 73 year old white male, with rheumatoid arthritis of approximately 11 months' duration, showed, early in the course of his illness, recurring attacks of pain and swelling which suggested the diagnosis of palindromic rheumatism. Five months prior to admission the acute attacks failed to subside and he showed increasingly severe pain, swelling and limitation of motion in the hands and wrists. After a 12 day period of study on the ward, he was given 100 mg. of progesterone by injection for 18 days. After 10 days of therapy there was some subjective improvement and at the time of completion of treatment, although there was only slight increase in motion, the pain and swelling were less prominent. Two weeks later the symptoms recurred with the original degree of severity. His sedimentation rate was markedly elevated and showed no significant change during or after therapy. The patient did not believe that a second course of treatment would be worth while and consequently no placebo could be administered.

Case 6. A 19 year old white male with very severe rheumatoid arthritis and rheumatoid spondylitis of six years' duration had had steady progression of the disease from the time of onset. Previous therapy had included x-ray, intravenous typhoid vaccine, Ertron, gold and synovectomy of one knee. At the time of admission to the hospital there was rigidity of the entire spine and deformity of most of the peripheral joints. An acute reaction was present in one wrist and knee. He was given 300 mg. of anhydrohydroxyprogesterone for 25 days and then 50 mg. of intramuscular progesterone for 14 days. No clinical change could be demonstrated. The

blood sedimentation rate varied between moderate and mild elevation during treatment, but was elevated to a considerable degree at the time therapy was discontinued.

Case 7. A 39 year old white woman had been suffering from rheumatoid arthritis for 20 years. Originally the involvement had been intermittent, but for three years she had shown persistent activity with gradually increasing deformity of the hands and feet. At the time of study, the patient had moderate activity of the disease with pain on motion and tenderness of hands and feet. She was given 300 mg. of anhydrohydroxyprogesterone daily for 10 days and 100 mg. of progesterone intramuscularly for 15 days. There was some slight degree of improvement in pain and stiffness which continued for three weeks after completion of treatment. The sedimentation rate was elevated and showed little change until near the completion of therapy at which time it showed some decrease. Two weeks after discharge, at which time the clinical improvement was even more manifest, the sedimentation rate was found to be markedly increased.

Case 8. A 50 year old white female had had rheumatoid arthritis for four years. The original episode was characterized by an intense inflammatory reaction in the joints which subsided after gold therapy, leaving some residual deformities in the hands and fingers. About seven months before admission, there was a severe recurrence of symptoms continuing up to the time of study. She was admitted on the metabolic ward and given 300 mg. of anhydrohydroxyprogesterone daily for 28 days. Some improvement in stiffness and swelling occurred, but pain and limitation of motion remained essentially unchanged. This was maintained for several weeks, but two months after discharge the disease had resumed its progressively downward course. The markedly elevated sedimentation rate showed no decrease during or following therapy.

Case 9. A 16 year old white girl had rheumatoid arthritis of five years' duration. There had been temporary improvement following a course of typhoid vaccine therapy, but no effect was evident after a second course or after treatment with gold, massive doses of vitamin D, physical therapy or repeated transfusions. Her course had been steadily progressive for one and one-half years prior to admission, and at the time of study there was marked involvement of the knees, fingers and elbows with pain, tenderness, and limitation of motion. She was treated with 150 mg. of intramuscular progesterone daily for 10 days. At the time of completion of therapy there was slight relief of pain, some increase in joint movement and minimal decrease in swelling, but two weeks following treatment the acute symptoms recurred. The sedimentation rate was markedly elevated and remained so throughout the course of treatment.

Case 10. A 25 year old white female first developed symptoms of rheumatoid spondylitis approximately 10 years ago. Involvement of the peripheral joints had been present for three years. At the time of this study there was complete ankylosis of the spine and signs of activity in the form of redness, swelling and pain in several of the peripheral joints. The patient was given progesterone intramuscularly, 150 mg. daily for three days and 200 mg. daily for 12 days. During the last seven days of therapy 800 to 1,000 mg. of ascorbic acid were given daily both by vein and by mouth. There was only minimal clinical improvement and the markedly elevated sedimentation rate remained unchanged.

Case 11. A 52 year old colored female had rheumatoid arthritis of 12 years' duration. At the time of this study, she had residual thickening of both wrists with almost complete immobility. There was fusiform swelling and tenderness of the left middle finger and painful limitation of motion of the left shoulder. She was given 150 mg. a day of anhydrohydroxyprogesterone for 14 days. There was marked clinical improvement including freer movement of both wrists which at the beginning of therapy were believed to be permanently ankylosed, but no change occurred in the

elevated sedimentation rate. Improvement remained manifest for the next several months despite laboratory evidence of continued activity. About one year after this treatment was given she had an acute exacerbation of symptoms, and an inert placebo was administered. A prompt clinical remission occurred which was manifest for the next three weeks. Treatment was discontinued with prompt return of symptoms and again there was relief after the institution of placebo treatment. At no time during this patient's course was there any depression of sedimentation rate which would suggest a true remission of her disease.

Case 12. A 60 year old white female had arthritis of 30 years' duration. Over this period of time she had experienced numerous acute attacks of arthritis involving the joints of all extremities, each one leaving her with a greater amount of residual deformity. At the time of study, in addition to the chronic deformities the patient had an acute involvement of both hands, the left wrist and both knees. She was treated for 21 days with 200 mg. of anhydrohydroxyprogesterone. There was no clinical improvement and the markedly elevated sedimentation rate remained essentially unchanged.

Case 13. A 60 year old white male had had rheumatoid arthritis for approximately 15 months. Prior to progesterone therapy he had received intravenous typhoid vaccine and gold without appreciable benefit despite the fact that the gold had produced a severe dermatitis. At the time of progesterone therapy there was acute involvement with redness, swelling and tenderness of practically all peripheral joints. He was given 200 mg. a day of anhydrohydroxyprogesterone and after a few days of therapy there was quite marked clinical improvement. This improvement continued for the next two and one-half weeks although the sedimentation rate remained markedly elevated. After 18 days an inert placebo was substituted. Improvement continued on this regimen, but when the placebo was discontinued for a few days a prompt and moderately severe exacerbation of symptoms occurred. Again there was improvement when placebo therapy was resumed which continued for the next three weeks. At no time was there any material change in the markedly elevated sedimentation rate.

Case 14. A 37 year old white woman's disease had commenced four years before with involvement of the hands. The condition progressed to involve the knees, toes, ankles and shoulders and for the six months prior to this study there had been steady progression with little effect from a short course of gold therapy. At the time of study, there was acute involvement of the left ankle and knee which were swollen, red, hot and tender. The patient was given anhydrohydroxyprogesterone 200 mg. daily for a total of 25 days. No clinical improvement resulted and there was some increase of the markedly elevated sedimentation rate. She has gone steadily downward since that time and her active disease has persisted. A course of gold, given several months after the progesterone therapy, proved to be equally ineffective in controlling her symptoms.

None of the patients showed any toxic symptoms except for Case 10 who received the largest dose of progesterone. This patient noted that there was some loss of head hair after the completion of treatment. There was no clinical evidence of fluid retention, and little gain of weight in any case. No unusual or unexpected menstrual changes occurred except in two patients. Case 4 had a normal expected period while receiving a daily dose of 50 mg. of progesterone. This patient was the only one to show any marked clinical improvement. One other patient, Case 10, had been amenorrheic for several months following a course of x-ray therapy for her spondylitis, and the vaginal smear showed lack of any estrogenic effect. A few days

after the completion of progesterone therapy, she had vaginal bleeding which simulated a normal menstrual period. Two of the patients believed that their appetites were markedly stimulated by the medication, but as both these patients were on controlled food intake for balance study this symptom could not be objectively evaluated. No patient showed any statistically significant change in blood pressure.

Laboratory Changes

In all of the patients there was some degree of anemia. In those who showed a progressive drop in hematocrit prior to therapy, the decrease was maintained at about the same rate during the administration of progesterone. In none of the cases was there a change in hematocrit values of sufficient degree to suggest any marked amount of hemodilution. No improvement in red cell count, hemoglobin or hematocrit was observed.

The white cell count in this group of patients ranged from three to twelve thousand. During treatment there was a rise in leukocytes in two patients and some depression in two others. In the remaining patients, no significant change was observed.

The percentage of circulating lymphocytes ranged from 16 to 53, with an average of 20 to 40 per cent in the majority of the patients. Five of the patients showed some decrease in lymphocytes during therapy, but in all but one case there was a return to the control level before therapy was stopped.

Serial total eosinophile counts were conducted in 10 of the patients. One patient showed a count of 33 per cubic millimeter, another a count of 225 per cubic millimeter, but the remainder had counts between 86 and 144 per cubic millimeter. A significant change during treatment occurred in only three patients. Case 6, who was most seriously affected by arthritis had a control level of 33 which rose to 110 during therapy. Patient 10 had control values of 90 with a rise to 400 during therapy and Case 9 showed a rise from 150 to 450 during the first few days of treatment with a return to control levels before therapy was discontinued. Except in patient 6, who had very severe debility and malnutrition there was no relation between the severity or chronicity of the disease and the eosinophile count.

The corrected sedimentation rate was elevated in all cases ranging from 16 to 42 mm. per hour in the male patients and from 28 to 44 mm. per hour in the females. In only one patient was there any significant decrease during treatment and lesser degrees of depression of the sedimentation rate could not be correlated with any clinical improvement.

Serial serum calcium, phosphorus and alkaline phosphatase determinations were made in 10 cases. The serum calcium was normal in all being between 9.6 and 11.3 mg. per 100 c.c. of blood. No change occurred except in patient 4 in whom there was a rise from 9.6 mg. to 12.0 mg. during treatment with a return to a level of 10.6 mg. one week after discontinuation of progesterone. Serum phosphorus values ranged from 3.4 mg. to 5.5 mg.

per 100 c.c., the higher values bearing no relation to age of patient or the severity of the arthritis. There was no significant change during treatment in any case. The alkaline phosphatase was, with one exception, normal averaging from 1.9 to 3.8 Bodansky units. Patient 6, age 19, who showed impaired growth and development, probably because of the severity of the disease during his puberal years, had a phosphatase level of 7.0 units. This rose to 10.2 units during treatment with anhydrohydroxyprogesterone and to 16 units after therapy with intramuscular progesterone. No significant change was apparent in any of the other patients. Urinary calcium excretion, with the patients on a known calcium intake, was studied in five cases. The control values were normal in all and there was no significant change during therapy.

Serum cholesterol partition studies were conducted at frequent intervals in eight patients and before and at the end of therapy in three others. The cholesterol values for all patients tended to be low, ranging from 90 to 145 mg. per 100 c.c. of blood with an average of 122 mg. The ratio of free to total cholesterol was elevated to over 0.40 in six of the patients and over 0.35 in three others. In five patients there was no appreciable change in total cholesterol or the free cholesterol/total cholesterol ratio during therapy. In one patient the change was equivocal. Changes in the other five patients were of a varying nature. Case 1 showed an increase in the ester and free portions in such fashion that the free/total ratio remained unchanged. Case 5 showed an elevation of both the total and free portions so as to give a rise in the free/total ratio. Case 7 showed a drop in ester fraction during therapy to give a higher free/total ratio. Case 8 gave a drop in total and in ester portions to give a rise in the free/total ratio. Case 10, who was studied on only one occasion before and once after medication, showed a rise in all the fractions of the cholesterol, that of the free being greatest and consequently giving a rise of the free/total ratio. Although none of these changes appears to be consistent, the most nearly constant change was an increase in the free/total ratio.

Creatine and creatinine determinations of 24 hour urine specimens were followed serially in eight patients. Creatinine values ranged from 0.7 to 1.2 grams in 24 hours and there was no appreciable change in any case during progesterone therapy. Creatine excretion was increased in three patients. In Case 1, it ranged between 0.1 and 0.23 gm. and there was no change during therapy. In Case 2, there was a range between 0.32 and 0.53 gm. during the control period with a drop during progesterone therapy to 0.1 gm. Case 6 showed levels of 0.3 to 0.4 gm. during the control period and this level of excretion was maintained throughout treatment. Amounts of creatine varying from 0.15 to 0.25 daily were excreted in three of the female patients, values considered to be normal in this sex. None of these patients showed any decrease in the excretion of creatine during therapy and in those patients who had minimal or barely measurable amounts of creatine present in their urine, no increase could be demonstrated.

Serum amylase determinations were conducted in three patients because of the suggestion of Schiller and Smith [18] that progesterone secretion may have an effect on the blood levels of this enzyme. In Case 7, amylase rose from control levels of 87 and 84 units to 158 and 133 units at the end of treatment. In Case 9, however, there was a drop from control levels of 81 and 98 to a level of 52 and then to 30 units at the end of treatment. In Case 10, the control levels were 37 and 41 with a drop to 16 during treatment, and a rise to 45 two days after treatment was discontinued. Fasting blood sugar determinations were conducted on two patients before and after progesterone therapy and in neither of these cases was any significant change discernible. In a third patient, an oral glucose tolerance test was conducted before and at the end of therapy. The blood sugar curves were essentially the same on both occasions.

Total urinary neutral 17-ketosteroid determinations were made in 13 of the patients. Values in all were low, in male patients ranging from 4.5 to 7.5 mg. in 24 hours, and in the female patients from 2.6 to 8.0 mg. in 24 hours. There was no appreciable difference in 17-ketosteroid excretion in either sex and no significant difference between the older and younger patients. Changes in 17-ketosteroid excretion during and after progesterone therapy were variable and of no marked degree. In those patients who had follow-up 17-ketosteroid examinations, there was a tendency for a slight rise in excretion. This most probably can be attributed to the improved nutritional status of the patients following their period of hospitalization.

Nitrogen balance study was conducted in eight of the patients. In four of the cases there was a very positive nitrogen balance during the control period believed indicative of previous wasting of protein. Two were approximately in balance during their control period, while the other two went into negative balance on an adequate protein intake. One of these patients, Case 6, was seriously affected and had very low 17-ketosteroid excretion levels. The other patient, however, was not seriously ill, had normal 17-ketosteroid levels for her sex, and was in good general condition. During the course of progesterone therapy, negative nitrogen balance resulted in a number of the patients. This occurrence which has been commented on by Abels and Dobriner [19] and by Albright [20] is now under further investigation. The only patient, Case 4, to show marked clinical improvement, was in balance during the control period and went into very negative nitrogen balance during her course of therapy. Other patients, however, went into negative nitrogen balance without showing any improvement in their clinical state.

Addendum

Recently there has appeared a report by Reich [21] upon the use of progesterone in rheumatoid arthritis. He administered 50 mg. of progesterone daily for 30 days, followed by small doses by mouth for two to seven weeks.

Of the 21 patients treated, four obtained excellent results, seven showed moderate improvement and only six failed to show any clinical relief. In none of his patients was there any change in sedimentation rate.

Summary

Fourteen patients with active rheumatoid arthritis have been treated with progesterone or anhydrohydroxyprogesterone for periods of 12 to 40 days. Definite clinical remission occurred in one patient on two separate occasions with each drug, but there was no decrease in sedimentation rate or significant increase in mobility of the affected joints. Moderate improvement took place in three other patients. In two of these a comparable remission followed the use of an inert placebo. Three patients were very slightly improved symptomatically but objective changes were minimal. In only one case did the sedimentation rate approach normal levels. Numerous laboratory studies were conducted, but there was no relationship between clinical improvement and change in the laboratory findings. Treatment with progesterone in the manner used here does not appear to be of any value in the treatment of rheumatoid arthritis.

BIBLIOGRAPHY

1. Hench, P. S.: Analgesia accompanying hepatitis and jaundice in cases of chronic arthritis, fibrositis and sciatic pain, Proc. Staff Meet., Mayo Clin. **8**: 430–436, 1933.
2. Hench, P. S.: Effect of jaundice on chronic infectious (atrophic) arthritis and on primary fibrositis, Arch. Int. Med. **61**: 451–481, 1938.
3. Thompson, H. E., and Wyatt, B. L.: Experimentally induced jaundice (hyperbilirubinemia), Arch. Int. Med. **61**: 482–495, 1938.
4. Gardner, F., Stewart, A., and MacCallum, F. O.: Therapeutic effect of induced jaundice in rheumatoid arthritis, Brit. Med. J. **2**: 677–680, 1945.
5. Hench, P. S.: The ameliorating effect of pregnancy on chronic atropic (infectious rheumatoid) arthritis, fibrositis, and intermittent hydroarthrosis, Proc. Staff Meet., Mayo Clin. **13**: 161–167, 1938.
6. Barsi, I.: A new treatment of rheumatoid arthritis, Brit. M. J. **2**: 252–253, 1947.
7. Editorial: Transfusions of blood from pregnant women for rheumatoid arthritis, J. A. M. A. **139**: 718, 1949.
8. Hughes, W.: Resistence in rheumatism, Ann. Rheumat. Dis. **3**: 89–100, 1942.
9. Sjövall, H.: Die Hormonausscheidung bei chronischer Polyarthritis des Weibes, Acta med. Scandinav. **117**: 69–88, 1944.
10. Cohen, A., Dubbs, A. W., and Myers, A.: The treatment of atrophic arthritis with estrogenic substance, New England J. Med. **222**: 140–142, 1940.
11. Freyberg, R. H.: Treatment of arthritis with vitamin and endocrine preparations; emphasis of their limited value, J. A. M. A. **119**: 1165–1171, 1942.
12. Dunn, C. W.: Present status of endocrine therapy in arthritis, M. Clin. N. Am. **24**: 1697–1708, 1940.
13. Touw, J. F., and Kuipers, R. K. W.: The treatment of affections of the joints with progestine, Acta med. Scandinav. **96**: 501–508, 1938.
14. Leblond, C. P.: Detoxification of progesterone derivatives in the liver, Am. J. M. Sc. **204**: 566–567, 1942.
15. Pearlman, W. H., and Cerceo, E.: The isolation of pregnanol-3 (gamma)-one, preg-

nanediol 3 (alpha), 20 (beta) and etiocholanediol-3 (gamma), 17 (beta) from the bile of pregnant cows, J. Biol. Chem. **176**: 847–856, 1948.

16. Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F.: The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone) (Compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis. Preliminary report, Proc. Staff Meet., Mayo Clin. **24**: 181–197, 1949.
17. Hamblen, E. C., Cuyler, W. K., and Hirst, D. V.: Urinary excretion of pregnanediol complex by males, Endocrinology **27**: 172–176, 1940.
18. Schiller, S., and Smith, O. W.: Serum diastase and its relation to estrogen metabolism in pregnancy and the menstrual cycle, J. Clin. Endocrinology **3**: 154–161, 1943.
19. Abels, J. C., and Dobriner, K.: Effect of progesterone on the nitrogen balance and on the circulating proteins of a normal man. Conference on Metabolic Aspects of Convalescence, Jos. Macy Jr. Found. **7**: 121, 1944.
20. Albright, F., and Reifenstein, E. C.: The parathyroid glands and metabolic bone disease, 1948, The Williams & Wilkins Co., Baltimore, Md.
21. Reich, N. E.: The use of large doses of progesterone in rheumatoid arthritis, Am. Practitioner **4**: 1–5, 1949.

STUDIES ON THE AGING HEART. I. THE PATTERN OF RHEUMATIC HEART DISEASE IN OLD AGE (A CLINICAL–PATHOLOGICAL STUDY) *

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Introduction

The heart in old age presents problems of the utmost clinical significance since this is the age when the heart most commonly begins to fail. That this is true of arteriosclerotic and hypertensive heart diseases is unquestionably accepted. Our present study gives evidence that rheumatic fever is also a significant and important etiological factor in heart disease and in congestive heart failure of old age. Improved management with resultant increased longevity as well as improved diagnostic acumen have both led to an increase in the number of clinically recognized cases of rheumatic heart disease in the latter half of life. Evidence to be presented also indicates the little realized importance of initial attacks of rheumatic fever and of clinical rheumatic activity in old age.

Purpose of This Study

1. Correlation of the incidence of rheumatic heart disease at Goldwater Memorial Hospital with data from other sources.

2. Analysis of the clinical features of rheumatic heart disease, especially as related to autopsy data at the Goldwater Memorial Hospital, a hospital engaged mainly in the investigation and treatment of chronic and old age diseases.

3. Determination of the diagnostic errors and pitfalls in order to facilitate diagnosis in old age.

Material

Two hundred sixty-three cases between the ages of 40 and 81 with autopsy records have been reviewed. Among these, 50 cases showed pathological signs (gross, microscopic, or both) of rheumatic heart disease. The clinical and pathological records of these cases were tabulated and analyzed (table 1). These 50 cases were from all medical services of the hospital.

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TABLE I

Pathological and Clinical Analysis of 50 Consecutive Autopsied Cases of Rheumatic Heart Disease

No.	Age	Sex	Cause of Death	Autopsy	Clinical Diagnosis	CHF Duration	R.F. History	Liver Clinical	Autopsy	Daily Digitalis	Rheumatic Clinical	Activity Autopsy	Murmurs	EKG	X-ray	Blood Pressure
1	42	F	RHD CHF	RHD M.V. PT	Same	5 yrs.	5 yrs.	1 finger	1600G LC	1½ grs.	EKG	Yes	S D	AV block P	PC	120/70
2	52	F	Gangrenous cystitis	Cystitis RHD M.V. R. myoc. RA	Same	None	No	NP	1500G FI CPC	None	None	No	S	Neg.	None	120/72
3	81	M	Lobar pneumonia	Pneumonia Bronchiectasis RHD M.V.	AHD Bronchiectasis	6 mos.	No	NP	1200G CPC Degen.	1½ grs.	EKG?	No	S	AV block WP	Neg.	180/100
4	71	F	Hemorrhage	RHD M.V. Luetic aortitis Rectal polyp	RHD M.V. Anemia Rectal polyp	3 yrs.	No	NP	Neg.	None	EKG?	No	S	Nodal rhythm	None	94/60
5	53	M	RHD CHF	RHD Act TV, PV, bicuspid Pulm. valve Dextra aorta Pulm. tbc. Septal defect	RHD M.V. Pulm. tbc.	Child-hood	27 yrs.	5 f	1700G CPC	1½ grs.	None	Yes	S	AF	MAT	140/80
6	42	F	RHD CHF	*Rt. vent. hypert.* RHD M.V. AV TV	Same	9 yrs.	10 yrs.	enl.	1320G CC	None	Yes	Yes	S D	AF Low voltage	Obsc.	—
7	50	M	Broncho-pneumonia	Bronchopn. Amyloid liver RHD M.V.	Bronchopn. R.A.	None	No	enl.	1800G Amyloid	None	Sed. rate?	No	None	None	None	120/70
8	50	F	Ca of stomach Post-operative shock	Ca of stomach RHD AHD M.V.	Ca of stomach AHD	Poor history	No	NP	1450G Congestion	None	None	No	S	None	None	—
9	73	M	Coronary failure	Coronary sclerosis AHD RHD M.V.	Coronary thrombosis	3 yrs.	No	2 f	1580G CPC	1½ grs.	No	No	S	AV block	None	136/74
10	41	F	RHD CHF	RHD M.V. MP Saddleback thromb. Cav. sin. thromb.	RHD M.V. Encephalitis	1 mo.	No	enl.	CPC	1½ grs.	Thrombi?	No	S D	ST elev.	MT	140/75
11	45	F	RHD CHF	RHD Act. M.V. TV MP	RHD Act. M.V.	3 yrs.	No	enl.	CPC FI	1½ grs.	Yes	Yes	S P	AF	MT	140/86
12	78	M	RHD CHF	RHD M.V. MP Ca of the lung	AHD Ca of the lung	1 yr.	No	2 f	1270G Neg.	1½ grs.	No	Yes	S	AF	enl.	120/65
13	43	M	RHD CHF SBE	RHD ACT. M.V. AV SBE	Same	1 yr.	No	2 f	CPC	None	Yes	Yes	S D	LAD	enl. HT	140/60

TABLE I—*Continued*

No.	Age	Sex	Cause of Death	Autopsy	Clinical Diagnosis	CHF Duration	R.F. History	Liver Clinical	Autopsy	Daily Digitalis	Rheumatic Clinical	Activity Autopsy	Murmurs	EKG	X-ray	Blood Pressure
14	40	M	RHD CHF	RHD M.V. AV	RHD HHD	1 yr.	30 yrs.	2 f	2340G CPC	1½ grs.	Yes	Yes	S D	LBBB T	enl.	170/110
15	76	M	RHD CHF	AHD RHD MT AV Ascites	AHD	3 yrs.	No	3 f	1080G CPC	1½ grs.	No	No	S	None	None	150/76
16	44	F	Acoustic neuroma	Lobar pneumonia Acoustic neuroma AHD RHD M.V.	Lobar pneumonia Cerebral accident	None	No	NP	1620G Acute congestion	None	No	No	None	None	None	100/64
17	48	M	RHD CHF	RHD AV M.V.	RHD M.V.	1 yr.	No	5 f	1520G CPC	Varied	No	No	S D	None	None	100/70
18	57	M	RHD CHF Post-operative shock	RHD M.V. AV Post-operative Gastrectomy	Peptic ulcer	Terminal	No	2 f	1220G Neg.	None	No	No	S	None	None	130/90
19	61	M	RHD CHF SBE	RHD SBE AV M.V. Encephalomalacia	Same	2 yrs.	30 yrs.	enl.	1350G Acute cong.	None	SBE	SBE	S D	P	enl.	177/89
20	48	M	RHD CHF	RHD Act. M.V. TV AV Adhesive peric.	RHD M.V. AV	3 yrs.	30 yrs.	enl.	1600G CPC	1½–3 gr.	Joints sed. rate	Yes	S D	AF	MAT	120/65
21	57	F	RHD CHF	RHD Act. M.V. PT	RHD Act. M.V.	40 yrs.	47 yrs.	enl.	1370G CPC	1½ grs.	Yes	Yes	S D	AF	MAT	150/90
22	63	F	RHD CHF	RHD Act. M.V. AV	RHD Act. M.V. AV	45 yrs.	50 yrs.	2 f	1650G CPC	1½ grs.	Yes	Yes	S D	AF	enl.	130/90
23	51	F	RHD SBE	RHD Act. AV M.V. TV SBE	Same	1 yr.	36 yrs.	NP	1250G Neg.	None	SBE	Yes	S D	AF	enl.	155/90
24	46	M	RHD CHF	RHD Inact. M.V. PT	RHD M.V. Lobar pneumonia	6 yrs.	27 yrs.	4 f	1390G CC	¼ gr.	No	No	S D	AF	MAT	100/60
25	53	F	RHD CHF	RHD M.V. AV TV Bronchopneumonia	RHD M.V. AV TV HHD	20 yrs.	48 yrs.	5 f	1920G CC	1½ grs.	No	No	S D	AF LAD	Hypert. Type	185/95
26	68	M	Cerebral accident	Encephalomalacia RHD M.V.	HHD	Unknown	Unknown	NP	—	None	No	No	None	LAD	enl.	190/110
27	53	F	RHD CHF	RHD M.V. AV Adhesive peric. Hydrothorax	AHD Pulm. fib. Pulm. embolism	1 yr.	None	enl.	CC	¼ gr.	No	No	S D	LAD AF	enl.	100/60

TABLE I—*Continued*

No.	Age	Sex	Cause of Death	Autopsy	Clinical Diagnosis	CHF Duration	R.F. History	Liver Clinical	Autopsy	Daily Digitalis	Rheumatic Clinical	Activity Autopsy	Murmurs	EKG	X-ray	Blood Pressure
28	53	M	RHD CHF	RHD Act. M.V. TV MP	RHD Act. M.V.	Many yrs.	Many yrs.	enl.	CPC	3 grs.	Yes	Yes	S D	RAD 10 AV block	MT	—
29	71	F	RHD CHF	RHD AV M.V. TV Adhesive peric.	HHD AHD	Many yrs.	None	enl.	CPC FI	1½ grs.	No	No	S	None	None	170/90
30	74	F	RHD CHF	RHD M.V. HHD	Same	1 yr.	58 yrs.	enl.	CPC	¾–1½ grs.	No	No	S D	RAD AF	MT	210/80
31	76	F	Postop. abdomino-perineal resection	RHD M.V. AV HHD	AHD Postop.	None	None	NP	Neg.	None	No	No	S	RSR	Neg.	148/88
32	52	F	Fract. femur Cerebral accident	Encephalomalacia RHD M.V. AHD Lipoid pneumonia	Fract. femur Pseudobulbar palsy Lipoid pneumonia	Many yrs.	None	NP	1100G CPC	None	No	Yes	S	None	None	170/110
33	62	F	Coronary insufficiency	RHD M.V. AHD	Diabetes mellitus Coronary thrombosis	1 yr.	None	enl.	CPC Fatty degen.	¾ gr.	No	No	S D	RSR	Neg.	178/70
34	43	F	Cerebral and lipoid pn.	RHD M.V. Glomerulonephritis Lipoid pneumonia	RHD Hemiplegia	Unknown	None	enl.	1400G CPC	1½ grs.	Yes	Yes	S D	RAD P	MT	—
35	78	M	Subarachnoid hemorrhage	Subarachnoid hemorrhage RHD M.V. AV	Subarachnoid hemorrhage AHD	4 yrs.	None	enl.	1330G	3 grs.	No	Yes	S D	AF VPC LAD	AT	174/70
36	62	F	Lymphosarcoma	Lymphosarcoma Cholecystitis RHD M.V.	HHD Avitaminosis Pyelonephritis	None	None	enl.	1800G CPC FI	None	No	No	S	None	None	140/70
37	42	M	SBE	SBE RHD M.V. AV Peric.	Same	8 yrs.	23 yrs.	enl.	2000G CPC	3 grs.	Yes	Yes	S D	10 AV block	MT	—
38	73	F	Cirrhosis of liver	Laennec cirrhosis HHD AHD RHD M.V. TV	Cirrhosis Diabetes mellitus HHD AHD	None	None	2 f	LC	None	No	No	S	Left vent. strain	enl.	210/90
39	62	M	RHD CHF	RHD Act. M.V. AV PT Encephalomalacia	AHD	1 yr.	40 yrs.	1 f	1475G CPC	1½ grs.	No	Yes	S	Left vent. strain	MAT	140/80

TABLE I—*Continued*

No.	Age	Sex	Cause of Death	Autopsy	Clinical Diagnosis	CHF Duration	R.F. History	Liver Clinical	Autopsy	Daily Digitalis	Rheumatic Clinical	Activity Autopsy	Murmurs	EKG	X-ray	Blood Pressure
40	53	M	Bronchopn. pulm. tbc.	RHD M.V. AV TBC. Bronchopneumonia	RHD Act. M.V. RA	None	18 yrs.	—	—	None	Yes	Yes	S D	RAD	None	120/60
41	45	M	RHD CHF	RHD M.V. AV + V	Same	3 yrs.	6 yrs.	enl.	CC	1½ grs.	Yes	Yes	S D	RAD AF	enl.	100/76
42	59	M	RHD CHF	RHD M.V. AV	Same	2 yrs.	3 yrs.	4 f	CC	None	Yes	Yes	S D	AV block WP AF	enl.	105/75
43	52	F	RHD CHF	RHD M.V. TV	Same	10 yrs.	None	4 f	1390G Acute cong.	1½ grs.	No	No	None	None	None	130/65
44	51	F	RHD CHF SBE	RHD M.V. SBE	Same	1 yr.	None	2 f	CPC	1½–3 grs.	No	SBE	S D	None	None	126/88
45	51	F	RHD CHF	RHD M.V. AV Bronchopneumonia	Same	3 yrs.	31 yrs.	3 f	1225G CPC	None	No	No	S D	AF	MT	98/74
46	78	M	Ca of lung	Ca of lung RHD M.V. AV MP	Ca of lung AHD	3 yrs.	None	2 f	CPC	3 grs.	No	No	S	AF	enl.	100/50
47	45	F	RHD CHF	RHD M.V. TV PT MP	RHD M.V.	3 yrs.	None	enl.	1540G CPC	1½ grs.	Yes	Probable	S D	AF	MT	—
48	52	F	RHD CHF	RHD M.V.	RHD M.V.	20 yrs.	40 yrs.	enl.	2700G CC	1½ grs.	No	No	S D	AF RAD	MT	—
49	59	F	Myocardial infarction	Myocardial infarc. RHD M.V.	HHD Diabetes mellitus Nephrosclerosis	None	None	NP	1700G Portal fibrosis	None	No	No	S	T	None	190/100
50	62	M	Ca of finger	Ca of finger RHD M.V.	Ca of finger RHD M.V.	None	Yes	NP	1700G Cong.	None	No	No	S	None	None	120/80

ABBREVIATIONS

Act.	Active
AF	Auricular fibrillation
AHD	Arteriosclerotic heart disease
AV	Aortic valvulitis
CC	Cardiac cirrhosis
CHF	Congestive heart failure
CPC	Chronic passive congestion
Cong.	Congestion
D	Diastolic
f	fingers
Fl	Fatty infiltration
enl.	Enlarged
HHD	Hypertensive heart disease
LC	Laennec cirrhosis
LAD	Left axis deviation
LBBB	Left bundle branch block
MAT	Mitral and aortic type
MP	MacCallum patch
MT	Mitral type
M.V.	Mitral valvulitis
NP	Not palpable
P	P wave abnormal
PC	Pulmonary conus prominent
Obsc.	Obscured by lung changes
PV	Pulmonic valvulitis
Peric.	Pericarditis
PT	Pulmonary thrombus
RHD	Rheumatic heart disease
RA	Rheumatoid arthritis
R. Myoc	Rheumatic myocarditis
S	Systolic
SBE	Subacute bacterial endocarditis
TV	Tricuspid valvulitis
WP	Wandering pacemaker
RAD	Right axis deviation

Incidence of Rheumatic Heart Disease in Old Age

White and Bland [1] reported three autopsied cases of rheumatic heart disease after the age of 80. Cabot [2] reported six patients aged 70 to 80 with mitral stenosis in a series of 4,000 autopsies. DeGraff and Lingg [3] reported six patients 70 to 80 years in total of 644 with rheumatic heart disease. Wartman and Hellerstein [4] in 2,000 autopsies found that the number of cases of rheumatic heart disease was 120 and among these 28 were above the age of 45. Other comparable necropsy studies in various cities have shown an incidence rate of rheumatic heart disease at all ages as follows: in Boston,[5] 5.5 per cent; in Atlanta,[6] 3.5 per cent; in Galveston,[7] 0.9 per cent; and in New Orleans,[8] 0.63 per cent. The present study includes 11 patients with rheumatic heart disease between the ages of 70 to 80 years and one of 81 years in a series of 263 consecutive autopsies.

Since this analysis showed altogether 50 proved cases of rheumatic heart disease between the ages of 40 to 81 in 263 consecutive autopsies, it may be said that at this chronic disease hospital, rheumatic heart disease in the aging patients (over 40) was found in 19 per cent of a series of autopsies.

Table II

Incidence of Rheumatic Heart Disease Found by Different Authors as Related to the Ages above 40, 45, 50, 60, Respectively

Wyckoff and Lingg (50)	5–10%
DeGraff and Lingg (40)	25%
Cohn and Lingg (45)	15.6%
Boas and Fineberg (50)	34%
Stone and Feil (50)	28%
Willius (50)	0.8%
Samways (60)	10%
Cabot (50)	30%
Levine and Fulton (50)	20%
Horns (45)	63%
White and Jones (40)	25%

A table of varied incidence is shown above and also in table 2. Figures must vary depending on the age to which they refer, on the climate and on the source of the materials; i.e., whether the survey is from general hospital or chronic disease hospital patients, general cardiac clinics, industrial populations, or life insurance statistics. It would be more instructive to bring all these factors to a common denominator. Unfortunately, for obvious reasons, this is not possible. It has to be added that different clinical and pathological criteria were used in the different studies and this also has to be taken into consideration in their comparative evaluation. In the present study, cases without definite anatomical and physiological valve impairment were not included. Nevertheless our figures indicate a higher incidence than other autopsy series figures. The reason for this is that Goldwater Memorial Hospital is an institution engaged in the study and treatment of chronic diseases and as such has a greater number of cardiac cases referred for admission than general hospitals.

Analysis of Autopsied Patients

Fifty consecutive cases from all services of this hospital with autopsy-verified diagnosis of rheumatic heart disease over the age of 40 are analyzed in detail in table 1. This table shows data on the correlation between the clinical and autopsy diagnosis, the cause of death, the duration of rheumatic fever, and congestive failure when it was present. It also indicates which cases showed rheumatic activity, clinically or at autopsy, what types of murmurs were present, and what the electrocardiographic and x-ray changes were. These data may be correlated with the data in the clinical-pathological study of 46 cases of mitral stenosis by Boas and Perla [9] over 20 years ago, the recent clinical study of 106 cases of mitral stenosis over the age of 50 of Baker and Musgrave [10] and two also recently published pathological studies of Rosenthal and Feigen [11] and Wartman and Hellerstein,[4] and the study of minor rheumatic fever cases by Poliakoff.[12]

1. *Congestive Heart Failure.* Evidences of congestive failure were present in 37 of the 50 cases. In 31 of the 50, congestive failure was due to rheumatic heart disease and was the chief cause of death. In six patients the congestive failure was apparently caused by hypertensive or arteriosclerotic heart disease with a minor rheumatic mitral lesion being coincidental.

Table III

Age Incidence of Rheumatic Heart Disease at Goldwater Memorial Hospital by Decades

40–50	14
50–60	17
60–70	7
70–80	11
81	1
Total	50

In the 31 dying with rheumatic heart disease and congestive heart failure, symptoms of cardiac disease were of less than three years' duration in 19, under 10 years' duration in 24.

In the ensuing discussion, it will be found convenient to group the 31 patients dying from rheumatic heart disease with failure, separately from the 19 with less advanced rheumatic lesions and no congestive failure of rheumatic etiology.

2. *Age.* The average age of the group was 57.3 years, range 40 to 81 years (table 3). There were 14 patients in the fifth decade, 17 in the sixth decade, 7 in the seventh decade, 11 in the eighth decade, and 1 in the ninth decade. Average age in the series of Boas and Perla [9] was 57.7 years.

In the 31 patients with advanced rheumatic heart disease, average age was 54.0 years, range 40 to 78 years.

3. *Sex.* There were 27 females with average age of 56.3 years and 23 males with average age of 58.8 years. Of the 31 advanced cases, 18 were females and 13 were males.

4. *Rheumatic History.* In our type of aged patient this is often difficult to evaluate especially in a chart analysis. In the 31 advanced cases, the ward histories contained note of rheumatic fever in 19 or 61 per cent. The time elapsed since rheumatic fever in these 19 cases was 3, 5, 6, 10, 16, 18, 19, 21, 27, 30, 31, 36, 40, 47, 48, 50, 58, and "many" years (table 4). In those with less advanced rheumatic heart disease a positive history was obtained in 40 per cent of the total. Boas and Perla [9] noted a positive history in 37 per cent, Baker and Musgrave [10] in 30 per cent.

5. *Rheumatic Activity.* Criteria of clinical activity, and indeed of pathological activity, are still not sufficiently standardized for general agreement. However, 16 of the cases studied were definitely considered to be active rheumatic heart disease while on the wards, because of fever, symptoms, sedimentation rates, blood counts, etc. In all 16, pathological study confirmed this diagnosis of rheumatic heart disease, active. A chart review suggests activity to us in four additional cases.

Activity of rheumatic infection in old age is not uncommon and would be found more frequently if sought with painstaking work-up. As in younger patients, congestive failure with poor response to therapy should excite suspicion of activity.

TABLE IV

Duration of Rheumatic Fever (When Known)

Under 10 years	3
10–20 years	4
20–30 years	2
30–40 Years	4
40–50 years	3
50–60 years	2
"Many" years	1
Total (known)	19

6. *Murmurs.* Murmurs, especially apical diastolic murmurs if present in a characteristic form are quite frequently pathognomonic of rheumatic heart disease. In the aged, however, they are absent in a larger percentage of proved cases than in the young. The classical opening snap and the rumbling low pitched mid-diastolic murmur are not found in every case. They are modified by underlying arteriosclerotic changes, by slowing of the blood stream, and by a number of other cardiac and extracardiac factors common to old age. Several authors have emphasized that in a certain percentage of cases no murmurs were found. It was also pointed out that in some other cases of mitral stenosis only a systolic murmur was audible.

In the present series, in four of the 50, no murmurs were heard clinically. None of these was diagnosed ante mortem. None was of sufficient severity to produce congestive heart failure. The lesion in each was confined to mitral valvulitis, inactive.

In 19 of the series of 50, systolic murmurs only were heard. The diagnosis of rheumatic heart disease was missed in 15 of the 19 because the murmurs were misinterpreted.

In 27 of the 50, systolic and diastolic murmurs were heard. Of these, 24 were correctly diagnosed ante mortem. In retrospect, more attention should have been paid by the examiners to the physical findings in the three undiagnosed cases.

The diastolic murmur of mitral stenosis in this age group is often absent, often evanescent, often localized to a small area of the chest. Auscultation must be performed in quiet surroundings, must be repeated, must be done before and after exercise, or after the administration of nitrites. It should be repeated in the forward bending or left lateral position and both with the diaphragm and bell type chest pieces, since the murmurs are sometimes low pitched as in the young, while at other times they are high pitched in character.

As to the other murmurs, apical systolic murmurs are often taken to be due to arteriosclerotic changes or to dilatation of the aorta. The typical murmurs of aortic insufficiency and stenosis are also diagnosed, sometimes erroneously in this age group, as being due to arteriosclerotic or luetic etiology when really they are of rheumatic origin.

TABLE V

Electrocardiographic Abnormalities in the Advanced and Less Advanced Cases of Rheumatic Heart Disease

EKG Abnormalities	Advanced Cases	Less Advanced Cases
Auricular fibrillation	14	3
Right axis deviation	5	1
A-V block	4	2
P wave changes	3	1
Wandering pacemaker	3	—
Nodal rhythm	—	1
Total	29	8
More than one abnormality	5	1

7. *Valves Involved.* Of the 31 advanced cases, 30 had mitral involvement. Of these 30, 14 had mitral and aortic valvulitis, seven had mitral valve involvement exclusively, six had involvement of mitral, aortic, and tricuspid valves, three had involvement of mitral and tricuspid valves, there were four with MacCallum patch, and four with pericardial involvement. Interestingly enough, the one case without mitral involvement was in a patient with congenital heart disease who showed involvement of the tricuspid and pulmonic valves only.

In the 19 cases of less advanced rheumatic heart disease, 15 involved the mitral valve only, three the mitral and aortic valves, one the mitral and tricuspid valves.

Our findings do not differ significantly from those of Stone and Feil [18] in an unselected age group.

8. *Electrocardiography.* Electrocardiograms were available in 25 of the 31 advanced cases. Twenty-four of these were abnormal (table 5), three showed P wave changes, five showed right axis deviation, four showed

auriculoventricular block, three showed wandering pacemaker, and 14 showed auricular fibrillation.

Of the 19 less advanced cases, seven showed abnormalities of the type commonly seen in rheumatic heart disease, three showed auricular fibrillation, two showed auriculo-ventricular block, one showed nodal rhythm, and one showed right axis deviation with high P_1.

9. *Roentgenographic Findings.* Twenty-four of the 31 advanced cases were studied by teleroentgenography. All were abnormal, eight were described as "mitral type," five as "mitral and aortic type," two as "hypertensive type," two others as "slightly enlarged," five were called "enlarged in all directions," one had "pericardial effusion," and one had "prominent pulmonary conus." One of the two with roentgen-ray findings described as "hypertensive type," did have hypertensive heart disease in addition to rheumatic heart disease.

TABLE VI

Associated and Incidental Diseases in Autopsy Proved Rheumatic Heart Disease Cases

A. Cardiac	Arteriosclerotic heart disease	5
	Hypertensive heart disease	13
	Congenital heart disease	1
	Luetic heart disease	1
	Bacterial endocarditis	5
B. Hepatic	Chronic passive congestion	27
	Cardiac cirrhosis	10
	Acute congestion	3
	Laennec cirrhosis	1
	Amyloid liver	1
	Chronic hepatitis	1
C. Pulmonary	Pulmonary infarct	5
	Bronchopneumonia	4
	Lobar pneumonia	1
	Lipoid pneumonia	2
	Hydrothorax	2
	Bronchogenic carcinoma	2
	Tuberculosis	2
D. Renal	Focal embolic glomerulonephritis	5
	Acute diffuse glomerulonephritis	1
E. Rheumatoid	Arthritis	3

In the 19 cases of less advanced rheumatic heart disease, teleroentgenograms were done in seven. Four were normal, two with hypertensive heart disease had enlargement of the left ventricle, one was described as "aortic type."

ASSOCIATED AND COINCIDENTAL DISEASES * (TABLE 6)

a. *Rheumatoid Arthritis.* Rheumatoid arthritis was present in three patients of the 50 autopsy proved rheumatic fever cases. Dawson's [14] figures indicate that 7 per cent of all cases of rheumatoid arthritis have rheumatic heart disease. In the three cases of this series, the lesion was confined

* As separate diseases these will be subjects of other parts of this study. Here they are treated only as correlated to cases of rheumatic heart disease.

to healed mitral valvulitis with congestive failure. All three were correctly diagnosed ante mortem.

b. *Coronary Artery Disease.* This was present in five. In three there was associated hypertension. Coronary artery disease with myocardial infarction was the cause of death in two cases. Coronary artery disease was a contributory cause of death in two additional cases.

c. *Hypertension.* Hypertension above 150/100 mm. of mercury was present in 13 cases or 26 per cent of the series. Seven of the 13 died from causes related to hypertension. There were three deaths from cerebral accident, two died with myocardial infarction, and two with hypertensive heart disease and congestive failure. A high incidence of hypertension in old age rheumatics has been emphasized in other studies. Musgrave and Baker [10] summarized the reported studies as showing frequencies of 30 to 58 per cent.

d. *Congenital Heart Disease.* One of our series had interventricular septal defect, dextra position of the aorta and bicuspid pulmonary valve. This 53 year old patient was a known rheumatic for 30 years and died in failure. In this patient the rheumatic valvulitis was confined to the tricuspid and pulmonic valves. The changed cardiac dynamics of this congenital lesion might explain the localization.

e. *Luetic Heart Disease.* One of our series died of acute hemorrhage from a rectal polyp. A diagnosis of rheumatic heart disease was made clinically. Autopsy revealed unsuspected luetic aortitis in addition.

f. *Subacute Bacterial Endocarditis.* Five of this series died with subacute bacterial endocarditis. Ages were 42, 43, 41, 41, and 61 years. Three had involvement of mitral and aortic valves, one had involvement of the aortic and tricuspid valves, and one of the mitral valve only. The correct etiology was diagnosed ante mortem in all five cases.

g. *Liver.* Clinical examination revealed liver enlargement in 38 of the total of 50 and in 29 of the 31 advanced cases.

Autopsy showed liver pathology in all 31 cases of advanced rheumatic heart disease. Chronic passive congestion was reported in 14. Cardiac cirrhosis was found in eight. Chronic passive congestion with fatty degeneration was present in three. Chronic passive congestion with central cirrhosis of hepatic cells was reported in two. Three showed acute congestion. One showed cirrhosis, probably of the Laennec type.

In the other 19 cases there was chronic passive congestion in five, chronic passive congestion with fatty infiltration in three, cardiac cirrhosis in two, amyloidosis in one, and chronic hepatitis in one.

h. *Pulmonary Complications.* Significant pulmonary complications, aside from chronic passive congestion, were found in 18. There were five cases of pulmonary infarct, four of bronchopneumonia, one of lobar pneumonia, and two of tuberculosis.

i. *Nephritis.* Aside from the typical renal lesions of the five cases of

subacute bacterial endocarditis, one patient was found at autopsy to have acute diffuse glomerulonephritis. This patient died, apparently of a cerebral accident.

Analysis of Diagnostic Errors in 50 Autopsied Cases

The 50 cases of rheumatic heart diseases came from all services of this hospital and had been seen by many different attending physicians and cardiologists. A correct diagnosis of rheumatic etiology was made in 31 or 62 per cent of all cases. In the 31 cases of advanced rheumatic heart disease, a correct diagnosis was made in 26 or 84 per cent.

In five advanced cases, a correct diagnosis was not made. In one 53 year old patient with a one year history of failure, a loud systolic murmur was heard over the entire precordium. A diastolic murmur, heard on one occasion, was not noted subsequently. There was no rheumatic history. Roentgen-ray showed enlargement of all dimensions. Electrocardiogram showed left axis deviation and auricular fibrillations. In retrospect the correct diagnosis might have been made if the isolated finding of a diastolic murmur had been followed up with repeated careful auscultation. The roentgen-ray finding of great cardiac dilatation in the absence of hypertension and nephritis might also have been more carefully weighed. Autopsy disclosed cardiac enlargement, mitral valvulitis, aortic valvulitis, and adhesive pericarditis. In a second case the loud respiratory sounds concomitant with bronchogenic carcinoma obscured the physical findings and the diagnosis. In three others, systolic murmurs were heard but the patients died soon after admission with no time for electrocardiographic or roentgen-ray studies.

Of the 19 cases with less extensive rheumatic heart disease, correct antemortem diagnoses were made by the examiners in only five. Of the 14 undiagnosed cases, 10 showed only healed mitral valvulitis at autopsy. Congestive heart failure was present in one of these 10 cases. This was related to a hypertension of 180/100 mm. of mercury. In one a transient diastolic murmur was ignored. In the others, chart review gives no clue to diagnosis.

Four of the undiagnosed cases showed more at autopsy than healed mitral valvulitis. One patient of 73, who died following operation for carcinoma, was found to have minimal aortic and mitral valvulitis at autopsy. Electrocardiogram, roentgen-ray, and physical findings ante mortem gave no hints of the valvular lesions. A second patient, age 78, dying of subarachnoid hemorrhage, showed mitral valvulitis, aortic valvulitis, rheumatic myocarditis (subacute) at autopsy. There was a systolic and diastolic murmur at the apex. Roentgen-ray showed "generalized enlargement, aortic configuration." Important diagnostic points were evidently neglected. A third patient, age 52, died of encephalomalacia and hypertensive heart disease. Autopsy showed mitral valvulitis, active-inactive. No murmurs

were heard. The electrocardiogram had shown only left axis deviation, and the roentgen-ray picture had been interpreted as generalized cardiac enlargement, hypertensive type. The fourth patient, with mitral and aortic valvulitis, died of bronchogenic carcinoma. The pulmonary râles of the mantle pneumonia around this lesion apparently blanketed the murmurs since no murmurs were heard in this case.

Discussion

Rheumatic heart disease of old age is an important clinical problem because of its high incidence as a disease and as a cause of death. It is more than a question of a minor inactive valvular lesion hastening the onset of failure in arteriosclerotic or hypertensive heart disease. Although age of acquisition is difficult to determine, we found a history of rheumatic symptoms under 10 years' duration in four of the 19 in whom the rheumatic history was clear (table 4). The duration of symptoms of congestive failure was less than three years in 17 of the 31 advanced cases. In 16 of the 31 advanced cases the typical signs of active carditis seen in younger patients were apparent. One reason for initiating the present study was the frequent clinical and pathological finding of this typical active rheumatic carditis. The other reason was to point out the diagnostic errors and difficulties encountered in this age group.

The clinical criteria used to designate cases as active lesions were the presence of febrile rheumatic recurrences, signs of acute carditis, in some cases subcutaneous nodules, and corroborative laboratory data (elevated sediment rate, leukocytosis, positive electrocardiographic findings). The pathological criteria were the generally accepted ones based on the works of Aschoff, Coburn, Talajev, Klinge, White, Swift, and others. They were as follows: more recent inflammatory reactions of the valves or other parts of the heart or serous membranes, fibrinoid swelling of the ground substance, focal necrosis, tendency to hemorrhages in these tissues, typical Aschoff bodies in the myocardium or MacCallum's patches in the form of mural granulomas. They were less frequently found than in the young, but more frequently than is the general opinion.

The valves most often involved were the mitral valves. All but one of the 50 cases had a mitral lesion. As pointed out before, the one case without a mitral lesion was a patient with congenital heart disease and involvement of the tricuspid and pulmonic valves only. Seventeen cases had aortic valvulitis, 10 had tricuspid valve lesions. Pericarditis was found in four cases, and MacCallum's patches also in four.

While the diagnosis of clinical activity was confirmed at post mortem in all 16 cases in which it was made, the diagnosis of rheumatic heart disease generally, and the valves involved particularly was made in 84 per cent of the more advanced rheumatic heart disease cases and in 62 per cent of the minor lesions. (See the preceding section on analysis of diagnostic

errors.) Errors of diagnosis have been reported from several institutions and they do occur in every hospital and in every group of patients. The errors can be broken up into the following subgroups: (a) cases having a murmur which was missed by fault or on account of poor conditions of examination or where the murmurs were blanketed by extracardiac conditions, bronchial or pulmonary râles or muffled by emphysema of the lungs, (b) cases in which the murmurs were noted but not properly evaluated, (c) cases in which on account of auricular fibrillation no murmurs were heard, (d) cases without murmurs because the valvular lesions were not of such a degree as to produce murmurs, (e) and finally, errors are committed because of the frequent findings of only systolic murmurs in the presence of mitral stenosis, or because the examiner does not bear in mind the possibility of rheumatic heart disease in this age group.

Of the associated diseases the frequency of hepatic and pulmonary diseases is striking. Autopsy showed liver damage in all 31 cases of advanced rheumatic heart disease. In the total of 50, the hepatic condition was diagnosed as cardiac cirrhosis in 10, chronic passive congestion with cellular necrosis and fatty degeneration in six, chronic passive congestion with central cirrhosis in four, Laennec type cirrhosis, chronic hepatitis and amyloid infiltration of the liver each in one instance. The cause of this frequency of liver lesions was partly due to preceding repeated heart failures and stasis, partly to the frequency and extent of anoxemia, and to the simultaneous presence of nutritional deficiencies.

Pulmonary lesions: The frequency of dyspnea and cyanosis with minimal cardiac lesions is a feature seen in rheumatic heart disease of old age. In this study it was found usually to be due to emphysema or pulmonary arteriosclerosis or to anemic anoxemia. Congestion, infarcts, and pneumonias are more frequent here than in rheumatic heart diseases of the young. In the 50 autopsied cases, 18 such instances were found, not counting chronic passive congestions. The pneumonias developed so often because the soil was favorable for bacterial invasion.[15] On the other side of the ledger were found the frequent cases of failure which develop in a well compensated heart after an attack of pneumonia or upper respiratory infection.

Arteriosclerosis of the senile or of the hypertensive type (hypertension was present in 26 per cent of the cases) was another associated disease frequently causing diagnostic difficulties for the pathologist as well as for the clinician. Some cases showed at autopsy, old arteriosclerotic changes with superimposed typical rheumatic lesions, others showed at one part of the heart, aorta, or coronary arteries degenerative changes, at other parts active rheumatic lesions. And finally it deserves to be noted that while the rheumatic lesions in most of the cases were such that old and recent lesions were present side by side, in four of the cases only the evidence of recent lesions was demonstrable.

Summary and Conclusions

1. A clinical-pathological study of findings in rheumatic heart disease in old age is presented.

2. Among 263 consecutive autopsies, 50 cases (19 per cent) of rheumatic heart disease between the ages of 40 and 81 (average 57.3 years) were found. Twenty-eight per cent of the group was between the ages of 40 and 50 and 72 per cent between 50 and 81 years. These figures indicate that rheumatic heart disease is quite frequent in old age. If sought with the same diligence as is rheumatic heart disease of the young, the correct diagnosis would be made more frequently.

3. A positive history of rheumatic fever was obtained in 19 of the 31 more advanced cases and in 20 of the total group (40 per cent).

4. In 16 of the 50 cases (32 per cent) clinical activity was found in the wards, and confirmed at necropsy. A chart review indicated activity in four more cases making a total of 20 patients (40 per cent) with signs of activity.

5. Rheumatic heart disease, active, was the chief cause of death in at least 32 per cent of the patients in this series. Rheumatic heart disease was the chief cause of death in 64 per cent of the total having this lesion.

6. Hypertension was found in 13 (26 per cent) of this series. Seven of these died from causes related to hypertension.

7. Pathologic lesions in the liver were found clinically in 76 per cent, and at necropsy in 86 per cent of the cases. Cardiac cirrhosis at autopsy was reported in 10 (20 per cent), fatty degeneration of the liver cells in six additional cases.

8. Significant pulmonary complications, aside from pulmonary congestions were reported in 18 (36 per cent). There were five cases of pulmonary infarct, five cases of pneumonia, and two of tuberculosis.

9. A correct diagnosis of rheumatic etiology was made in 62 per cent of the total series and in 82 per cent of the 31 more advanced cases.

10. Causes of errors in the cases not diagnosed correctly are analyzed.

BIBLIOGRAPHY

1. White, P. D., and Bland, E. F.: Mitral stenosis after 80, J. A. M. A. **116**: 2001–2004, 1941.
2. Cabot, R. C.: Facts on the heart, 1926, W. B. Saunders, Philadelphia.
3. DeGraff, A. C., and Lingg, C.: The course of rheumatic heart disease in adults, Am. Heart J. **10**: 459–477, 1935.
4. Wartman, W. B., and Hellerstein, H. K.: The incidence of heart disease in 2000 consecutive autopsies, Ann. Int. Med. **28**: 41–65, 1948.
5. Gelfman, Raymond: The incidence of acute and subacute bacterial endocarditis in rheumatic heart disease, Ann. Int. Med. **19**: 253–255, 1943.
6. Clairborne, T. S., and Wolff, B. P.: Rheumatic heart disease; postmortem studies, South. M. J. **34**: 684–689, 1941.

7. Decherd, G. M., Jr., and Herrmann, G. R.: Rheumatic heart disease in Texas, Texas State J. M. **39**: 229–231, 1943.
8. Bruno, F. E., and Engelhardt, H. T.: A clinico-pathologic study of rheumatic fever and rheumatic heart disease in the white and Negro races, New Orleans M. and S. J. **95**: 234–238, 1942.
9. Boas, E. P., and Perla, D.: Mitral stenosis after fifth decade, Am. J. M. Sc. **120**: 529–538, 1925.
10. Baker, L. A., and Musgrave, D.: A study of mitral stenosis in patients who survived the age of 50, Ann. Int. Med. **26**: 901–912, 1947.
11. Rosenthal, J., and Feigen, I.: Pathology of the mitral valve in the older age groups, Am. Heart J. **33**: 346–361, 1947.
12. Poliakoff, H.: Mild rheumatic reaction in Coast Guard recruits, Am. J. M. Sc. **213**: 37–40, 1947.
13. Stone, C. S., and Feil, H. S.: Mitral stenosis; clinical and pathological study in 100 cases, Am. Heart J. **18**: 53–62, 1933.
14. Dawson, M. H.: Incidence of rheumatic heart disease in rheumatoid arthritis, Nelson Loose Leaf Medicine, 1937, v.
15. Kaufman, P.: Relationship between nutritional deficiencies, contributory diseases, and resistance to infection, Bull. N. Y. Acad. Med. **20**: 414–415, 1944.

CLINICAL EVALUATION OF DISODIUM SUCCINATE, INCLUDING A REPORT ON ITS INEFFECTIVENESS IN TWO CASES OF SEVERE BARBITURATE POISONING AND SOME TOXICOLOGIC NOTES ON OTHER SUCCINATE SALTS *

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The significance of succinic acid in biologic oxidation and reduction is not fully understood. That it may be important is indicated by the fact that most normal tissues contain succinic dehydrogenase, which is very active and can account for the rapid oxidation of substrate amounts of succinate in tissue slices in vitro.[1] Furthermore, the presence of succinate in the Krebs cycle can explain its rôle as a catalyst in the oxidation of carbohydrates and fats by certain tissue homogenates in vitro.[2] The following scheme of relationships is generally accepted[3]:

$$\text{succinate} + \overset{\text{oxidized}}{\text{succinic dehydrogenase}} \rightarrow \text{fumarate} + \overset{\text{reduced}}{\text{succinic dehydrogenase}}$$

$$\overset{\text{reduced}}{\text{succinic dehydrogenase}} + O_2 + \frac{\text{Cytochrome}}{\text{system}} \rightarrow \overset{\text{oxidized}}{\text{succinic dehydrogenase}}$$

In 1939, Quastel,[4] investigating the mode of action of barbiturates, found that this class of compounds depressed the R. Q. of brain tissue and inhibited the utilization of glucose and lactic and pyruvic acids. However, succinic acid oxidation was not inhibited.

This observation lay dormant from a clinical point of view until 1943 when Soskin and Taubenhaus[5] gave 22 grams of disodium succinate as a 10 per cent solution intravenously over a period of five hours to a patient who had taken 3.5 grams of Seconal and Allonal and had not responded to 1083 mg. of picrotoxin given over a period of two to three days. A dramatic recovery ensued. This work was followed by experimental work in rats, and these observers found that disodium succinate could diminish the duration of barbiturate anesthesia in these animals.

While Quastel's work has been repeated and confirmed, the work of Soskin and Taubenhaus has not been regularly confirmed, although in man

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Barrett [6] has evidence to show that disodium succinate is an effective analeptic in barbiturate depression. Along experimental lines, most of the work [7, 8, 9] shows that disodium succinate does exert a protective and analeptic effect in barbiturate anesthesia, but it is much less marked than indicated by the earlier report of Soskin and Taubenhaus. Some workers claim the analeptic effect is the result of diuresis and enhanced excretion of the drug.[10] Shorr [11] suggested that the disodium succinate may be of benefit in barbiturate poisoning only when the acid-base balance is upset, and then the benefit is derived from the sodium ion alone.

Aside from the action on the nervous system, Proger [12] has proposed other actions for the succinate ion. He reported that the injection of disodium succinate into anesthetized dogs could prevent the electrocardiographic changes induced by anoxia. Total oxygen utilization was not increased, but there was an increase in A–V oxygen difference, and this was accompanied by a fall in cardiac output.

Furchgott and Shorr [13] working with tissue slices, obtained quite different results. These investigators found that the succinate ion will cause significant increase in oxygen uptake by a variety of tissues when it is present in substrate concentration (44 to 88 mg. per cent). This increased oxygen uptake is chemically the equivalent of the conversion of succinate to fumarate. Catalytic effects were not observed except occasionally with kidney slices. The conversion of succinate to fumarate per oxygen atom utilized may yield one-half to one-third of the energy liberated by the oxidation of glucose. However, these authors found this energy to be unavailable for energy-requiring metabolic processes in the tissues which they studied in vitro. Moreover, when present in such substrate concentrations, the succinate competed with normal substrates for the available oxygen and the succinate oxidation predominated. At low oxygen tensions, succinate, although increasing oxygen uptake, actually decreased CO_2 production; along with this fall in CO_2 there was decreased production of acetylcholine by brain, urea by liver, high energy phosphate by cardiac and smooth muscle, and ammonia by kidney. If these results on tissue slices in vitro may be applied to intact animals, the use of succinate may be dangerous in the presence of impaired blood supply.

In humans, Barrett [6] has found that the intravenous administration of disodium succinate increases the depth and frequency of respiration and produces a flushing of the blush areas. His dosage schedules were variable (up to 60 grams) and determined empirically, but he noted no significant blood pressure changes or any adverse effects.

If the succinate ion can act as (a) a catalyst and effect an increased A–V oxygen difference, (b) an easily oxidized material when normal metabolic pathways are blocked, and (c) a vasodilator, it might be useful as medication under conditions of tissue anoxia and diminished blood supply, e.g., cor pulmonale, coronary artery insufficiency, peripheral vascular disease. Furthermore, if the succinate ion has an anti-barbiturate action, it would be

of interest to observe its effect on the hypotensive action of the barbiturates. It was the object of this study to examine the effects of intravenous disodium succinate upon various forms of tissue anoxia and the barbiturate-induced blood pressure fall in human subjects.

METHODS

This study was carried out on the Third (N.Y.U.) Medical Division, Goldwater Memorial Hospital, Welfare Island.

I. *General Effects:* To assess the general effects on humans, a group of 40 patients was selected. Their ages varied from 40 to 70 years, and they had no evidence of circulatory insufficiency of any sort. There was no evidence of any acute illness at the time the medication was administered. The distribution of patients according to diagnosis was:

Rheumatoid arthritis	16
Generalized arteriosclerosis	9
Central nervous system syphilis	4
Parkinson's disease	2
Postero-lateral sclerosis	2
Lupus erythematosus	1
Chronic exfoliative dermatitis	2
Polycythemia vera	2
Laennec's cirrhosis	2

Initially, one gram of disodium succinate was administered intravenously over a period of five minutes, and the skin color, temperature, pulse, blood pressure, and electrocardiogram were observed over a 24-hour period. All subjective complaints were recorded.

The dose of disodium succinate was then increased by one gram increments until a total of 5 to 6 grams was given at the rate of one gram per minute. Such dosage, it was calculated, would bring the succinate ion concentration into the range of catalytic concentration when equilibrium between blood and tissue spaces was established. More rapid administration was tried, using 2 and 3 gram doses at the rate of 2 grams per minute in some patients.

II. *Effect on Patients With Circulatory Insufficiency.* Ten patients with manifestations of circulatory insufficiency (cardiac and peripheral) were given disodium succinate in 5 gram doses at the rate of one gram per minute either daily or every other day for five doses. Note was made of skin color, temperature, oscillometer readings, and subjective improvement in the peripheral vascular group. In the cardiac group, pulse rate, electrocardiographic and blood pressure changes were noted.

III. *Anti-Barbiturate and Catalytic Actions:* (A). Since the succinate ion is supposed to have specific antibarbiturate action, 11 patients with hypertension were narcotized with 0.6 gm. of sodium amytal given in 0.2 gm. doses orally at hourly intervals. The blood pressure reaction was followed, and when it became stabilized, 5 grams of sodium succinate were injected intravenously at the rate of one gram per minute. The blood pressure and

electrocardiographic changes and degree of responsiveness were noted for six hours.

Through the courtesy of Dr. William S. Tillett, Director of the Third (N. Y. U.) Medical Division, and the coöperation of Dr. Barbara Parker and Dr. Frederick Hanold of the Psychiatric Medical Service and the Drug and Formulary Committee, Bellevue Hospital we were enabled to test the effectiveness of sodium succinate in two patients deeply poisoned by the ingestion of large amounts of barbiturate and non-responsive to ordinary stimulants or the convulsant drugs commonly used in the therapy of barbiturate poisoning.

(B). If the succinate ion can increase A–V oxygen difference and lessen cardiac output, and increase the dissociation of oxyhemoglobin, it should be of value in chronic cor pulmonale. Three patients with convincing clinical, x-ray, and electrocardiographic evidence of chronic cor pulmonale were given courses of intravenous injections of disodium succinate, consisting of five daily injections of 5 grams, given at the rate of one gram per minute. Electrocardiograms and ability to walk were used as indices of changes.

(C). Similarly, disodium succinate should prevent the electrocardiographic changes induced by exercise in subjects with coronary insufficiency. Seven patients who developed characteristic ST segment and T-wave changes during the Master test [14] were given 5 grams of disodium succinate intravenously at the rate of one gram per minute to see if these electrocardiographic changes could be prevented.

(D). If lactic acid is formed during the anaerobic phase of carbohydrate break-down in muscle work, the administration of disodium succinate should hasten the removal of this metabolite, since this process is dependent upon adequate oxygen supply. The exercise performed was vigorous flexion and extension of the fingers of one hand, and blood from the antecubital vein of that extremity was used. Five grams of disodium succinate were administered, given at the rate of one gram per minute. The work performed before and after succinate administration was as nearly identical as such voluntary effort could be. Lactic acid was determined by the method of Barker and Summerson.

IV. *Toxicity Studies:* The sodium content of disodium succinate is 28 per cent. In certain disease states where succinate use might be desirable, adverse effects might be anticipated from the intravenous administration of such large amounts of sodium. It was therefore decided to compare the toxicity of some other succinate salts with the disodium salt.

Disodium, monosodium, and ammonium succinate were administered intraperitoneally and intravenously to seven to eight week old female white mice of 15 to 20 grams weight, to determine the LD_{50} and the effect of speed of administration and concentration of solution upon the lethal dose.

The LD_{100} was approximated by starting at a dosage of 9 gm./kilo, and decreasing this level by units of 1.5 gm./kilo. At the LD_{100}, the dosage was

decreased by 0.5 gm./kilo units until an LD_{50} was reached. Two mice were used for each intravenous dosage level, and eight mice for the intraperitoneal route.

Results

I. *General Effects:* In the human subjects, only the 30 per cent solution of disodium succinate was used. The pH varied from 7.0 to 8.4 and the injection rate was set at one gram per minute. About 20 seconds after injection begins, the subject usually coughs. About a minute after injection is started, patients note an ammoniacal taste and a sense of burning in the pharynx. About three minutes after injection, a few have complained of pounding in the head, substernal oppression, and a burning sensation all over the body. A flush starting around the nose and lips begins about this time and rapidly spreads to involve the face and neck, becoming quite marked. There is some acceleration of the pulse and a rise of 10 mm. of systolic and diastolic blood pressure. The flush lasts about 20 minutes. The constant flushing dose is 5 grams given in five minutes. If three grams are given in this time, a flush appears in about half the cases. No change occurs in the temperature or color of the extremities. As measured by the oscillometer, there are no changes in blood flow. No electrocardiographic changes have been noted in these subjects. No benefits in symptoms or course of the underlying disease states were reported by patients or observed by us.

II. *Circulatory Insufficiency:* Table 1 summarizes the results in a group of 10 patients with manifestations of circulatory insufficiency:

Table I

Diagnosis	No. of	Objective Findings	Subjective Findings
Arteriosclerosis obliterans and gangrene	3	No change in area of gangrene	No relief of pain
Arteriosclerosis obliterans	2	No change in skin color, temperature or oscillometer readings	No relief of night cramps; no increase in ability to walk
Buerger's disease	2	No change in skin color, temperature or ulcers	No relief of pain or increase in ability to walk
Angina pectoris	3	No change in E. C. G., pulse rate, or blood pressure	No decrease in frequency attacks

The dose and mode of administration of the disodium succinate were detailed previously under the section "Methods."

III. *Anti-Barbiturate and Catalytic Actions:*

(A) Anti-Barbiturate Action: In all 11 hypertensive patients the administration of sodium amytal induced a drop in blood pressure. Administration of the disodium succinate was followed in all cases by a prompt rise in blood pressure which persisted for one to two hours. In seven patients this rise was slight, not reaching the pre-narcosis level. In one patient who had previously had a sympathectomy and later died of malignant hypertension,

the blood pressure rise exceeded the pre-narcosis level. The details are given in table 2.

An analeptic action (unrelated to blood pressure changes) was noted in half the cases, and was characterized by definite but slight increased responsiveness for about 10 minutes after the injection of the succinate. In two cases, this increased responsiveness was quite marked (both patients had mental deterioration from cerebral arteriosclerosis) and lasted 45 minutes. Continuous infusion of 15 grams of disodium succinate as a 5 per cent solution over a 90-minute period was ineffectual in three cases.

TABLE II

The Effect of Disodium Succinate on the Antipressor Action of Barbiturate (Sodium Amytal) in Essential Hypertension

Patient	Pre-Narcosis Blood Pressure*	Narcosis Blood Pressure*	Post-Succinate B. P.*	Duration of Succinate Effect
				Minutes
H. K.	190/100	165/70	180/100	80
G. M.	200/140	190/124	230/150	60
F. S.	230/140	200/135	210/140	55
D. P.	200/100	140/70	200/90	55
T. R.	190/95	130/80	160/100	80
G. K.	250/160	210/150	250/150	90
R. E.	180/110	140/90	160/110	115
W. B.	188/120	160/110	170/120	60
E. S.	200/120	180/100	180/110	75
E. C.	200/110	130/80	230/150	Myocardial infarct
H. K.	190/100	180/80	190/90	60

* mm./Hg.

(B) No analeptic action was observed with disodium succinate in the two cases of profound barbiturate intoxication. The details follow.

The first patient, a 64 year old man, ingested 40 tablets of sodium alurate. Upon admission to the hospital three hours later, he was in coma with cyanosis, circulatory collapse, and absence of all reflexes. Large amounts of barbiturate were recovered from the gastric washing.

The shock was successfully treated with intravenous fluids and continuous oxygen by tracheal catheter. Despite picrotoxin, caffeine and benzedrine, there was no relief of the coma.

Consequently about 24 hours after the ingestion of the barbiturate, it was felt that it would be in order to try disodium succinate. Forty c.c. of a 30 per cent solution (12 gm.) of disodium succinate were given intravenously over a 20 minute period. No response was noted except for a transient flush, tachypnea, and a slight blood pressure rise (10 mm. Hg systolic and diastolic). Further therapy was deemed inadvisable because of the presence of bilateral basal pulmonary râles.

The patient was maintained on oxygen and intravenous fluids. Five days after the ingestion of the alurate the patient regained consciousness. At this time there was no evidence of residual nervous system damage.

The second patient was a 35 year old man who swallowed 100 Tuinal capsules (300 grains). When first seen the patient had been in coma for 36 hours. He had made no response to picrotoxin, benzedrine, or caffeine. There was absence of all

deep and superficial reflexes. Blood pressure was 140/60, and patient was being maintained on intravenous fluids and continuous oxygen.

An infusion of disodium succinate was started and 72 gm. were administered by intravenous drip over a six hour period. No definite analeptic action was noted, though there was definite flushing of the blush areas and tachypnea while the medication was being administered. Mild pulmonary edema developed toward the end of the infusion.

After five days of supportive therapy (about five and one-half days after ingestion of the drug), the patient regained consciousness without residual neurologic damage.

(C) Anoxic Anoxia (Chronic Cor Pulmonale): No effect, either immediately after completion of the injection, or a day after completion of the course of injections, was seen in the three patients. Neither their resting blood lactic acid levels nor the lactic acid levels following exercise were altered by the injection of disodium succinate (table 4).

(D) Effect on the Master Two-Step Test: In only one of the seven patients in which ST segment and T-wave changes developed on exercise were such changes apparently prevented by intravenous succinate administration. This one exception was an individual who was not equally tachypneic after both exercise tests, so that exact comparison is not possible.[15] Table 3 summarizes these effects.

TABLE III

Effects of Disodium Succinate

Effects	No. of Patients	Subjective Findings	Objective Findings
Analeptic	11 (Essential hypertension)		5 were more responsive, 11 had blood pressure rise after fall had been induced by sodium amytal
A-V oxygen dissociation			
1. Bronchiectasis, emphysema, cor pulmonale	3	No improvement in dyspnea or ability to walk	No change in cyanosis or E.C.G.
2. Coronary insufficiency	7		Did not prevent E.C.G. changes on Master 2-step test.

(E) Effect on Lactic Acid Production: In six of 12 patients, lactic acid production after succinate administration and exercise was less than without succinate. In three of these six, the decrease was marked. In the remaining six, lactic acid production remained unchanged in three, slightly increased in two, and markedly increased in one. There was no apparent circulatory impairment in the exercised extremity, nor could the results be correlated with the primary diagnosis. Table 4 presents these data in detail.

It has been stated [16] that one of the methods of differentiating primary from secondary polycythemia lies in the blood lactic acid response to exercise. In primary polycythemia exercise is supposed to induce a fall, whereas in secondary polycythemia exercise produces the usual rise in blood lactic acid.

Two patients with polycythemia, one primary, the other secondary to chronic bronchitis and emphysema were studied. In both, exercise induced a distinct rise in blood lactic acid. Neither the level reached after exercise nor the subsequent decline during rest was much influenced by the administration of the disodium succinate. The last two cases in table 4 represent these patients.

TABLE IV

Effect of Disodium Succinate on Blood Lactic Acid Levels

Patient	Age	Diagnosis	Resting Lactic Acid Level In Mg. %	Lactic Acid after Exercise In Mg. %	After Succinate In Mg. %	After Exercise with Succinate In Mg. %
B. M.	70	Generalized arteriosclerosis	5	15	4	8.5
H. L.	75	Generalized arteriosclerosis	9	28	12	19
G. S.	48	Thromboangiitis obliterans	9	43	13	19
F. R.	61	Cor pulmonale	6	30	6	25
L. Z.	39	Luetic aortic insufficiency	6	20	6	15
J. B.	70	Generalized arteriosclerosis	8	23	9	17
C. G.	67	Generalized arteriosclerosis	10	22	8	22
W. B.	75	Generalized arteriosclerosis	2	12	3	13
J. T.	40	Diabetes mellitus	8	13	9	16
J. K.	61	Generalized arteriosclerosis	16	21	11	19
H. K.	60	Postero-lateral sclerosis	9	14	7	19
T. H.	44	Heart disease, unknown etiology	8	31	9	34
R. F.	50	2° Polycythemia	16	54	10	42
R.		1° Polycythemia	8	23	21	35

IV. *Toxicity Studies:* The following tabulation gives the LD_{50} of disodium, monosodium and ammonium succinate administered as 30 per cent solution to white mice at the rate of 0.1 c.c. per minute.

Material	pH	LD_{50}
30% disodium succinate	7.0	4.5 gm. /kilo
30% ammonium succinate	5.8	1.25 gm./kilo
30% monosodium succinate	5.8	1.5 gm./kilo

A speed-dose relationship was noted in determining the toxicity of these compounds. For example, the LD_{50} of monosodium succinate is 1.5 gm./kilo., given at the rate of 0.1 c.c. per minute. If the speed of injection is doubled, all the animals die at this dose. Similarly, on intraperitoneal administration, if the LD_{50} is diluted with 4 volumes of water, only an occasional animal dies. A similar relationship in regard to the flushing dose was noted in humans.

In white mice, monosodium succinate is three times and ammonium succinate four times as toxic as the disodium salt. The mode of death (generalized convulsions) was the same with all the compounds, and would seem to be a specific effect of the toxicity of the succinate ion rather than a function of the pH of the solution or the ammonium ion.

V. *Adverse Effects:* Disodium succinate has been intravenously administered by us altogether about 300 times. Adverse effects were noted in three instances as follows:

Case 1. A 52 year old male patient with rheumatoid arthritis (in whom there was no evidence of any valvular lesion or coronary insufficiency) developed a marked tachycardia with dyspnea and bilateral basal râles following the administration of 4 grams of disodium succinate in five minutes. This lasted about 15 minutes, and disappeared without treatment.

Case 2. A female patient, aged 59, who had hypertension and electrocardiographic evidence of old myocardial infarction was given sodium amytal to note the blood pressure response. There was considerable drop in blood pressure (from 200/100 to 130/60) but she had no symptoms. Ten minutes after the injection of 5 grams of disodium succinate, she developed severe interscapular pain with the clinical and electrocardiographic picture of myocardial infarction and clinical recovery in five weeks.

Case 3. A 50 year old male patient with cirrhosis of the liver and generalized arteriosclerosis, whose electrocardiogram was normal and who had no symptoms or signs of heart disease, was given 0.33 gm. of disodium succinate in 30 seconds. He began to cough, became pulseless, and died in a few minutes despite resuscitative measures. The mode of death was that of sudden cardiac standstill. Autopsy showed an old myocardial infarction.

Because the detailed pharmacology of the succinate ion is still unknown, any explanation of these adverse effects must be in the realm of speculation. The work of Furchgott and Shorr on tissue slices [13] suggests one explanation for the apparent toxicity in the intact organism. It is quite conceivable that in Cases 1 and 3, before mixing and diffusion could be effective, a high succinate ion concentration reached the myocardium. In Case 1, temporary myocardial failure may have been induced by the "anoxia" resulting from the consumption of much of the available oxygen by the succinate rather than by the normal energy producing substrates. In Case 3, the myocardial anoxia may have been even more severe because of the co-existent coronary artery disease. Another possibility is that the sudden cardiac standstill may have been the result of some deleterious action of the succinate ion on the medullary centers.

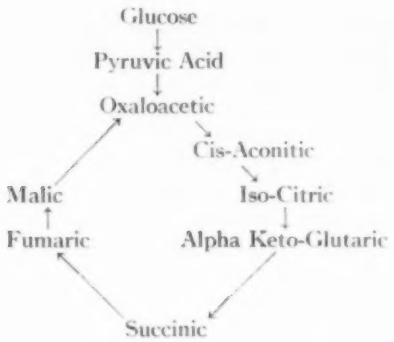
In Case 2, a complicating factor was added by the induction of a relative hypotension by sodium amytal. However, this was well tolerated by the patient, and it was not until after the succinate was administered that the patient developed any signs or symptoms. Presumably the combination of diminished coronary flow from the relative hypotension and coronary artery narrowing with the oxygen-depriving action of the succinate ion was sufficient to precipitate the myocardial infarct.

In connection with our observations in Cases 1 and 3 it was with interest that we noted the recent report by Dwyer, Kronenberg and Saklad [17] of the development of severe angina pectoris during the injection of sodium succinate in a 65 year old female who was being given the drug for the relief of leg pain attributed to arteriosclerotic peripheral vascular disease. Electrocardiographic changes noted after the injection included slight depression of the ST interval in Lead I and CF_4 and T_3 inversion. After five days another electrocardiogram showed T_3 upright and T_2 of greater amplitude.

General Discussion

If the Krebs cycle represents the main pathway of carbohydrate and possibly protein and fat metabolism in man, then succinic acid occupies a strategic position in energy liberation.

Succinic acid is in the middle of the cycle, in a position where it can yield considerable energy by further oxidation and yet past the initial portion of the cycle where oxygen lack or enzyme system injury might bring to a halt the liberation of energy. From its position in the cycle it would seem that, as an easily utilizable carbohydrate, succinic acid would be of use in situations where the supply of glucose and oxygen was limited, or where the enzyme systems controlling the degradation of cis-aconitic acid were disturbed. That such is the case in the utilization of glucose by brain tissue in vitro is indicated by the work of Quastel.[4] Whether or not this obtains in muscle or other tissue is not known.



On the other hand, the work of Furchgott and Shorr [13] tends to show that succinate is inactive when added in catalytic concentration to tissue slices excepting kidney. In substrate concentration in brain, kidney, liver, cardiac and smooth muscle, the succinate ion interferes with normal processes by successfully competing for the available oxygen. Under conditions of anoxia, therefore, the administration of succinate may be harmful. Perhaps this offers an explanation for the adverse effects which were observed in the three cases previously described. It is conceivable that, in the course of injection, before mixing and diffusion could be effective, the concentration of succinate in the blood reaching the heart and brain was high enough to offer competition in these tissues for the available oxygen.

The value of the succinate ion in barbiturate intoxication in humans is an unsettled question. Its use as an analeptic in short-acting barbiturate anesthesia is no guarantee that it would be effective in cases of poisoning with the longer acting barbiturates. Before one could be sure of any

analeptic action in such instances, a series of carefully studied cases would be needed, in which reliable information was available as to the total amount of barbiturate ingested, the blood level of barbiturate, and the urinary excretion of either unchanged barbiturate or degradation products therefrom. At present, chemical methods for the determination of barbiturates are not exact, and critical studies of the effect of succinate on barbiturate levels have not been made. Our experience with two deeply poisoned subjects, narcotized with long acting barbiturates is not encouraging.

If the succinate ion does not accomplish that which its position in the Krebs cycle indicates that it might, perhaps some of the other intermediary carbohydrates might be found effective. Their pharmacology is still quite unknown, and even if it is only speculation which suggests that they be tried, their possibilities are nevertheless engaging.

Conclusions

1. Disodium succinate has some anti-barbiturate action. It was without analeptic effect in two instances of deep prolonged barbiturate coma in man.
2. Save for the blush areas, it has no significant vasodilating action.
3. If disodium succinate acts as a catalyst in increasing A–V oxygen difference, such is not manifest in increasing work performance, or preventing electrocardiographic changes in myocardial anoxia. It may diminish lactic acid production during exercise, but as yet this is uncertain.
4. Disodium succinate should be used with caution whenever there is a history or evidence of heart disease.
5. Monosodium and ammonium succinate are more toxic than the disodium salt. At present their toxicity precludes clinical study.

We are grateful for the technical assistance of Mr. Robert White and Mrs. Victoria Salas Aguilar, and we are indebted to Dr. Gerald Lo Grippo and Mrs. Vera Golbey, B.A., for the performance of the toxicity tests in mice.

BIBLIOGRAPHY

1. Elliot, K. A. C.: Intermediary metabolites and respiratory catalysis, Physiol. Rev. **21**: 267–306, 1941.
2. Krebs, H. A.: The intermediary stages in the biological oxidation of carbohydrate, Advances in Enzymology **3**: 191–252, 1943.
3. Potter, V. R.: Biological energy transformations and the cancer problem, Advances in Enzymology **4**: 201–256, 1944.
4. Quastel, J. H.: Respiration in the central nervous system, Physiol. Rev. **19**: 135–183, 1939.
5. Soskin, S., and Taubenhaus, M.: Sodium succinate as an analeptic for barbiturate poisoning and in the control of the duration of barbiturate anesthesia, J. Pharmacol. and Exper. Therap. **78**: 49–55, 1943.
6. Barrett, R. H.: The analeptic effect of sodium succinate on barbiturate depression in man, Current Research in Anesthesia and Analgesia **26**: 74–81, 105–113, 1947.
7. Pinschmidt, N. W., Ramsey, R. H., and Haag, H. B.: Studies on the antagonism of sodium succinate to barbiturate depression, J. Pharmacol. and Exper. Therap. **23**: 45–52, 1945.

8. Beyer, K. H., and Latven, A. R.: An evaluation of the influence of succinate and malanate on barbiturate anesthesia, J. Pharmacol. and Exper. Therap. **21**: 203–208, 1944.
9. Lardy, H. A., Hansen, R. C., and Phillips, P. H.: Ineffectiveness of sodium succinate in the control of duration of barbiturate anesthesia, Proc. Soc. Exper. Biol. and Med. **55**: 277–278, 1944.
10. Corson, S. A., Koppanyi, T., and Vivino, A. E.: Effect of succinate and fumarate in experimental barbiturate poisoning, Current Research in Anesthesia and Analgesia **24**: 177–191, 1945.
11. Shorr, E.: Treatment of barbiturate poisoning, Am. J. Med. **1**: 93–103, 1946.
12. Proger, S.: The use of respiratory catalysts, particularly succinic acid, in tissue anoxia, Bull. New England M. Center **5**: 80–85, 1943.
13. Furchgott, R. F., and Shorr, E.: The effect of succinate on respiration and certain metabolic processes of mammalian tissues at low oxygen tensions in vitro, J. Biol. Chem. **175**: 201–215, 1948.
14. Master, A. M.: The electrocardiogram after exercise—a standardized heart function test, U. S. Naval M. Bull. **40**: 346–351, 1942.
15. Christensen, B. Chr.: Electrocardiographic changes in man during voluntary hyperventilation, J. Clin. Investigation **25**: 880–889, 1946.
16. Best, C. H., and Taylor, N. B.: Physiological basis of medical practice, p. 17, Third Edition.
17. Dwyer, C. S., Kronenberg, S., and Saklad, M.: Anginal syndrome during sodium succinate therapy, Ann. Int. Med. **31**: 148–153, 1949.

STREPTOCOCCAL ANTIHYALURONIDASE TITERS IN THE SERA OF PATIENTS WITH RHEUMATOID ARTHRITIS AND GLOMERULONEPHRITIS *

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Recent observations on streptococcal antihyaluronidase in human sera have shown that the concentration of that antibody is elevated above the normal in acute rheumatic and streptococcal infection. Within the clinical groups mentioned it has been found that the mean antihyaluronidase titer is higher in acute rheumatic fever than following streptococcal infections, and that the range of such titers in the former disease extends above the range found in the latter.[1, 2, 3, 4]

These observations have directed interest to the question of antibody levels to this streptococcal enzyme in two other diseases: glomerulonephritis, because of its similarity to rheumatic fever in its frequent epidemiologic relationship to streptococcal disease, and rheumatoid arthritis, because of the importance in its pathogenesis of fibrinoid degeneration of collagen.

These diseases have been studied in the past in relation to streptococcal antigens, particularly in comparison with rheumatic fever. It has in general been found in the case of neutralization tests available in earlier years—antistreptolysin and antifibrinolysin—that glomerulonephritis showed a high rate of incidence of elevated titers in such tests, similar to that found in active rheumatic fever,[5, 6, 7] but that the incidence of such elevated titers in rheumatoid arthritis was only about 30 per cent.[7, 8, 9] In the case of streptococcal agglutination reactions the incidence of elevated titers was high,[8, 10] but this has been considered to be due to a non-specific factor in the serum of rheumatoid arthritis which tends to lower the suspension stability of bacterial cells.[11] The more easily interpreted streptococcal serologic data have, then, grouped glomerulonephritis with rheumatic fever, in contrast to rheumatoid arthritis. Some additional interest in the current investigation lay in the fact that the streptococcal antigen involved in the antihyaluronidase tests was an enzyme attacking the ground-substance of the tissue involved in the pathologic process common to these diseases.

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Methods and Materials

Clinical Material: The patients whose sera are included in this study were seen in an active stage of their disease in the hospitals from which this study is reported. The patients with rheumatoid arthritis and glomerulonephritis were all seen in the winter and spring of 1948–49, and because of year-to-year variations in the distribution of antibodies to streptococcal antigens in the community [12] only sera drawn during the same interval were included in the case of normal subjects, patients with active rheumatic fever and those convalescing from acute streptococcal infection.

The criteria used for the diagnosis of active rheumatic infection are given elsewhere.[2] The criteria for a diagnosis of active glomerulonephritis included clear-cut history, hematuria, gross albuminuria, elevated erythrocyte sedimentation rate and the classical symptoms of this disease.

Rheumatoid arthritis, as considered in this study, was taken to include only those cases in which there was a characteristic insidious onset of joint swelling, involving symmetrical joints, accompanied by weight loss and other signs of chronic systemic disease with a definite tendency toward the production of joint deformity and an increased sedimentation rate. The activity of the process was evaluated on the basis of the degree of swelling, joint effusion, stiffness and height of the sedimentation rate.

The Serologic Tests: Specimens of serum were prepared and frozen as they were obtained, until all the sera to be included had been collected. They were then thawed and three simultaneous serologic tests were performed for all sera. The antistreptolysin test was done, for comparison with results reported in the earlier literature, by a method [13] adapted slightly from Todd's original method, for better comparison with the antihyaluronidase tests. Two antihyaluronidase tests were performed, for the sake of corroboration of the results: the mucin-clot-prevention test as described elsewhere [2] and the turbidimetric test by a technic described in a current paper.[14] To ensure validity of the comparisons a specimen of gamma globulin derived from pooled human serum was included in each rack of each test as a standard preparation of the antibodies.

Results

A definite diagnosis of active rheumatoid arthritis was made in 45 cases. The antihyaluronidase titers (M.C.P.) of the 45 specimens of serum ranged from less than 8 to 1,024, the greatest frequency of titers occurring between 32 and 128. The geometric mean titer of this group was 72. The antistreptolysin titers ranged from less than 8 to 256, with a mean value of 48, and a similar concentration of relatively greater frequencies in the range of 32 to 128.

The 54 patients with glomerulonephritis, although all had the disease in its active form, included a number in whom the acute episode had persisted for a few weeks, because of less active contact with this group of patients than with the rheumatic patients. In this group the antihyaluronidase titers

(M.C.P.) ranged, again, between less than 8 and 1,024, but the greatest concentration of frequencies was at 128 to 512, and the geometric mean titer was 146. The antistreptolysin titers for this group showed a similar range and maximum frequency and a mean titer of 128. These results, and others, are summarized in table 1, which affords a direct comparison of the geometric mean titers of the antibodies as measured by the three tests in all the clinical groups.

On examination of the mean antihyaluronidase titers in table 1, it can be seen that the mean titer observed in rheumatoid arthritis was somewhat higher than that found in the normal population and even in convalescents from acute streptococcal infection, but was lower than that found in active rheumatic fever. In glomerulonephritis the mean antihyaluronidase titer was found to be higher than in the rheumatoid and post-streptococcal groups, and substantially closer to the mean of patients with active infection, but not as high as the latter.

TABLE 1

Mean Titers of Streptococcal Antihyaluronidase and Antistreptolysin in Several Clinical Groups of Children as Observed during the Winter of 1948–1949

	Antihyaluronidase	Antistreptolysin
Normal	22.5	36.5
Scarlet fever, acute	12	17
Scarlet fever, convalescent	30	96
Rheumatoid arthritis	74	48.5
Glomerulonephritis	146	128
Rheumatic fever	360	292

The mean antistreptolysin titers showed, in general, the same relations as the antihyaluronidase, with some difference in that the mean titer was found to be only slightly higher in patients with glomerulonephritis than in the post-streptococcal group.

The geometric mean titer gives only an approximate indication of the relations and differences involved. In the present case this is especially true because a considerable number of sera in the entire group had titers below the threshold of the test (less than 8). Accordingly, the distributions of titers within each interval of titration of serum are indicated for each clinical group in figure 1. This figure contains a graph for each clinical category, in which the abscissae are serial twofold dilutions of serum, and each ordinate gives the percentage of patients within that category whose titer is as high as the corresponding titer or higher. Such cumulative percentage-frequencies afford a graphic demonstration of the similarities and differences among the distributions of titers.

On examination of figure 1 it is seen that the graphs of antistreptolysin titers show smaller differences among the clinical groups than do the antihyaluronidase titers. In the former it can be seen that the antistreptolysin titers found in rheumatoid arthritis did not differ substantially from the normal distribution, except that fewer sera had titers in the lowest range.

The cumulative frequencies of antistreptolysin titers in scarlet fever, glomerulonephritis and rheumatic fever show small differences among these groups, with a tendency toward the occurrence of progressively higher titers in the order named.

The antihyaluronidase titers show somewhat wider differences among the clinical groups. The frequent occurrence of very low titers among normal subjects and patients with brief streptococcal infection (this ob-

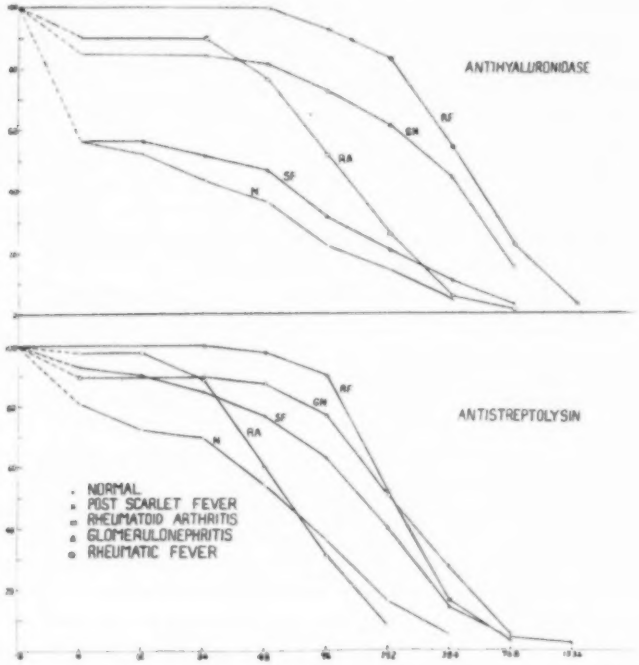

FIG. 1. Cumulative percentage-frequencies of occurrence of antistreptolysin titers and antihyaluronidase titers in normal children, convalescents from scarlet fever, and patients with active rheumatoid arthritis, glomerulonephritis and rheumatic fever, as observed in the winter of 1948–1949. In each graph titers are plotted against the percentage of subjects within the clinical group showing that titer or higher.

servation is discussed elsewhere [12]) sets these somewhat apart from the distributions in the other three diseases. In rheumatoid arthritis fewer low titers were found, but the upper end of the distribution resembled that found among normal subjects and patients convalescent from scarlet fever. The distributions of antihyaluronidase titers in glomerulonephritis and rheumatic fever were fairly similar in the range of higher titers, the greater frequency

of which distinguishes these two clinical groups from the others. The distribution of these titers in glomerulonephritis differed from that found in rheumatic fever, however, in the lower ranges, in that very low titers were seen to occur in the former disease but not in the latter.

Discussion

The data presented above would appear to indicate quite clearly that the pattern of antihyaluronidase titers in rheumatoid arthritis is distinct from that found in rheumatic fever. The measurable titers are in general distributed in proportion to those found after uncomplicated streptococcal infection, with a somewhat smaller tendency to occur in the higher titers than is the case in the post-streptococcal group. The low antihyaluronidase titers in rheumatoid arthritis in comparison with rheumatic fever are quite comparable to the lower antistreptolysin titers reported here and in earlier studies reviewed above, and with the relative antifibrinolysin titers reported in the earlier literature.

The comparison of the titers found in glomerulonephritis to those we have found in the same year in rheumatic fever is, however, less simple. The distribution of the measurable titers in glomerulonephritis is fairly comparable to that which we have found in rheumatic fever during the same year, in the case of both antibodies. In spite of this, the mean titers are lower in the case of glomerulonephritis, because a number of very low titers were found in that disease but not in rheumatic fever. The occurrence of some very low titers in glomerulonephritis resembles the picture found after acute streptococcal infections, whereas the distribution of higher titers resembles the situation in rheumatic fever. It is not possible at this time, and with the relatively small number of cases studied, to resolve this apparent paradox. The degree of similarity between the frequency distributions of antihyaluronidase titers in glomerulonephritis and rheumatic fever does not affect the limited usefulness of this test toward laboratory diagnosis in rheumatic fever, since the two diseases do not offer a problem in differential diagnosis. However, this partial similarity of distributions does have implications as to the possible significance of the relatively higher antihyaluronidase titers in active rheumatic fever. In an earlier discussion of this subject it was pointed out that this relatively higher range of antihyaluronidase than antistreptolysin titers in active rheumatic fever, in comparison with acute streptococcal infection, might well be due to special circumstances of the serologic reaction to an antigen produced in small quantities over a prolonged period of contact between the streptococcus and the tissues of the rheumatic host. The partial similarity of distributions of relative antihyaluronidase titers in a different disease, but one similar to rheumatic fever in its epidemiologic relations to the hemolytic streptococcus, would seem to lend some support to this possible explanation.

Summary

Streptococcal antihemolysin and antihyaluronidase have been measured in the sera of patients with rheumatoid arthritis and glomerulonephritis. The antihyaluronidase and antistreptolysin titers in the former disease were found to be quite distinct from those in active rheumatic fever. In glomerulonephritis differences were found from the distribution in active rheumatic fever in that a number of low titers were encountered in the former. The distribution of the higher titers in glomerulonephritis was, however, found to be fairly similar to those found in rheumatic fever during the same year.

We are indebted to Dr. Henry L. Barnett of The New York Hospital for a number of the sera of patients with acute glomerulonephritis.

BIBLIOGRAPHY

1. Quinn, R. W.: Antihyaluronidase studies of sera from patients with rheumatic fever, streptococcal infections, and miscellaneous non-streptococcal diseases, J. Clin. Invest. **27**: 471, 1948.
2. Harris, T. N., and Harris, S.: Studies in the relation of the hemolytic streptococcus to rheumatic fever. V. Streptococcal antihyaluronidase (mucin-clot-prevention) titers in the sera of patients with rheumatic fever, streptococcal infection, and others, Am. J. M. Sc. **217**: 174, 1949.
3. Harris, T. N., Harris, S., and Nagle, R.: Studies in the relation of the hemolytic streptococcus to rheumatic fever. VI. Comparison of streptococcal antihyaluronidase with antibodies to other streptococcal antigens in the serum of patients with rheumatic fever and acute streptococcal infection: mucin-clot-prevention test, Pediatrics **3**: 482, 1949.
4. Friou, G. J.: Further observations of an inhibitor in human serums of the hyaluronidase produced by a strain of hemolytic streptococcus, J. Infect. Dis. **84**: 240, 1949.
5. Tillett, W. S.: The occurrence of antifibrinolytic properties in the blood of patients with acute hemolytic streptococcal infections, J. Clin. Invest. **14**: 276, 1935.
6. Boisvert, P. L.: The streptococcal antifibrinolysin test in clinical use, J. Clin. Invest. **19**: 65, 1940.
7. Winblad, S.: Studies in hemolytic streptococcal fibrinolysin, antifibrinolysin and antistreptolysin, with particular reference to rheumatic fever, Acta. path. Scandinav. 1941, Supp. 44.
8. Blair, J. E., and Hallman, F. A.: Streptococcal agglutinins and antistreptolysins in rheumatoid arthritis, J. Clin. Invest. **14**: 505, 1935.
9. McEwen, C., Bunim, J. J., and Alexander, R. C.: Bacteriologic and immunologic studies in arthritis. III. Results of various immunologic tests in different forms of arthritis, J. Lab. and Clin. Med. **21**: 465, 1936.
10. Keefer, C. S., Myers, W. K., and Oppel, T. W.: Streptococcal agglutinins in patients with rheumatoid arthritis and rheumatic fever, J. Clin. Invest. **12**: 267, 1933.
11. Wallis, A. D.: Rheumatoid arthritis. II. Non-specific serologic reactions, Am. J. M. Sc. **212**: 716, 1946.
12. Harris, S., and Harris, T. N.: Serologic response to streptococcal hemolysin and hyaluronidase in streptococcal and rheumatic infection, J. Clin. Invest., in press.
13. Harris, T. N.: Studies in the relation of the hemolytic streptococcus to rheumatic fever. III. Complement fixation with streptococcal nucleoproteins in sera of patients with rheumatic fever and others, J. Exper. Med. **87**: 57, 1948.
14. Harris, S., and Harris, T. N.: The measurement of neutralizing antibodies to streptococcal hyaluronidase by a turbidimetric method, J. Immunol. **63**: 233, 1949.

THE NON-INFECTIOUS NATURE OF THE GUILLAIN-BARRÉ SYNDROME WITH A POSSIBLE EXPLANATION FOR THE ALBUMINO-CYTOLOGIC DISSOCIATION *

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THE Guillain-Barré syndrome is a clinical entity which is not often diagnosed although its occurrence is not uncommon. The chief reason for this is the failure of all attempts to isolate an etiologic agent and also the multiplicity of synonyms by which this form of neuritis is known. Infectious polyneuritis, Guillain-Barré syndrome, acute polyneuritis with facial diplegia, Landry's ascending paralysis, are but a few. To date there have been 25 names attached to this clinical picture. It is our intention not to further confuse the issue but rather to present two cases fulfilling the criteria of the Guillain-Barré syndrome, which were not of an infectious nature, and to discuss some of the factors which might account for the characteristic spinal fluid findings.

This disease is not a new one. Osler,[1] in 1892, described the first case under the name of "acute febrile polyneuritis" and noted its similarity to Landry's ascending paralysis. Several other case reports appeared in the succeeding 15 years but it was not until 1916 that important additions to the clinical picture were made. Patrick [2] reported two cases of facial diplegia with multiple neuritis, thus focusing attention on the cranial nerves, and in the same year Guillain, Barré and Strohl [3] first noted the high protein and low cell count in the spinal fluid—the albumino-cytologic dissociation—and emphasized the favorable prognosis of the disease. However, in 1918, Bradford, Bashford and Wilson,[4] and later Casamajor,[5] reviewing their experiences in the British and American armies respectively, found a fairly high mortality rate—about 25 per cent. From then on, the disease has been recognized more frequently, with a new name given to it by each succeeding observer.

Until recently, all the evidence pointed toward an infectious etiology of this syndrome. The type of infection initiating this course of events varies greatly; the syndrome has been known to follow in the course of acute upper respiratory infections, pneumonia, encephalitis, measles, mumps, scarlet fever, influenza, varicella, botulism, tuberculosis, and syphilis. Recently, infectious hepatitis and infectious mononucleosis were also found to be precipitating illnesses. In fact, Hiller and Fox [6] have suggested that a heterophile antibody determination be done in every case of the Guillain-Barré syndrome.

* Presented before the New Jersey Neuropsychiatric Association, April 21, 1948.

In a clinical complex in which a definite etiologic agent cannot be demonstrated, it is quite logical to look for causes other than infections. Thus, the syndrome has also been seen in cases of serum sickness, sulfonamide poisoning, cervico-dorsal arthritis, diabetes and artificial fever. Dietary deficiencies and poisoning by heavy metals are also possible etiologic factors.

In a syndrome with such widely divergent precipitating causes it is remarkable that the clinical picture is as constant as it really turns out to be. Guillain, Barré and Strohl,[8] in their original paper, laid down certain criteria which, in their opinions, had to be met:

1. Albumino-cytologic dissociation.
2. Preponderance of motor weakness over sensory disturbances, the latter mostly of subjective nature.
3. Remarkably rapid and complete recovery despite the initial serious appearance.

This last point has been the subject of much discussion. Guillain,[7] as late as 1936, stated that none of his cases died, yet mortality figures from other reliable clinics [5, 9, 10] vary from 20 to 40 per cent. Guillain and Barré were probably dealing with a benign form of the disease whereas other workers have seen the disease in its more serious manifestations, often terminating in death. An important factor in the prognosis in any case is the localization of the lesion. If the upper cord and the bulbar areas are involved the prognosis is much worse than if the changes are limited to the peripheral nerves of the lower extremities.

The clinical syndrome is a diversified, but characteristic, one. Therefore, we shall present a composite picture as it appears in the literature and from personal experience.

The onset is usually heralded by some upper respiratory infection. Mild aching pains in the back and legs and headache are the usual prodromata. The latent period varies from a few days to several months, but usually two or three weeks. The earliest neurological symptoms are referable to the sensory system and are characteristically limited to the distal portions of the extremities, such as paresthesias and numbness of the hands and feet. Shortly after the onset, the motor signs develop, consisting of bilateral symmetrical weakness and later paralysis. The proximal portions of the limbs are chiefly involved. Once developed, the motor signs completely overshadow the sensory changes. They vary from slight weakness to complete quadriplegia save for slight wriggling of the fingers and toes. When the trunk, diaphragm or intercostal muscles are involved, the prognosis is grave, as the chief cause of death is from respiratory paralysis. There is loss of reflex response and sensory impairment as well. Cranial nerve involvement occurs in a great percentage of cases, involving chiefly the facial nerve unilaterally or bilaterally. In the latter case the diagnosis of facial paralysis is quite difficult to establish. Other cranial nerve abnormalities consist of

blurring of vision, dysphagia, dysphonia, palatal weakness, tinnitus, nystagmus, etc.

Temperature elevation is not marked, especially after the first week. A mild tachycardia may be noted. Electrocardiographic changes indicative of toxic myocarditis have been reported.[11]

The spinal fluid findings have been the subject of discussion for many years. The characteristic high spinal fluid protein without cellular increase has been considered a requirement for the diagnosis by the French authors. Some writers have stated that a normal spinal fluid may be present but in these cases it has been felt that subsequent examinations would probably have revealed the characteristic changes. In general, the protein level varies from 80 to 800 mg. per cent and may remain elevated for years. Those cells that are present are usually all lymphocytes. A slight increase in the spinal pressure has been found, in most cases varying from 150 to 200 mm. of water.

The course of the disease is extremely varied, extending from three weeks to two years. As mentioned previously, this is not a benign disease, since the mortality rate varies from 14 to 42 per cent. The average mortality has been approximately 20 per cent. In children, deaths are rare.

In the differential diagnosis of the Guillain-Barré syndrome, there are two important diseases to consider—poliomyelitis and diphtheritic polyneuritis. In poliomyelitis there are no sensory changes. The paralysis is spotty and confined to single muscle bundles, whereas in the Guillain-Barré syndrome the paralysis is bilaterally symmetrical and involves large muscle groups. Also, in the latter disorder, there are apparently no muscle spasms. There are no epidemics of the disease and most of the cases occur in the colder months of the year following respiratory infections. Further, in 35 to 50 per cent of the cases of the Guillain-Barré syndrome, one finds cranial nerve involvement, whereas in poliomyelitis this occurrence is much rarer.

The resemblance to diphtheritic polyneuritis is quite close but nose and throat cultures and the history of contact are diagnostically important. The clinical pictures may be identical, even to paresis of accommodation, which is a characteristic of diphtheritic palsy.

One cannot discuss the problem of diphtheritic polyneuritis without commenting on its importance and prevalence during the recent war. Several comprehensive reviews [12, 13] have stressed the fact that cutaneous diphtheria is often overlooked and the diagnosis is missed entirely until neuritic or radicular symptoms have developed. Even then the true relationship between the cutaneous lesion and the polyneuritis is often not realized.

The differentiation of diphtheritic polyneuritis from the Guillain-Barré syndrome may be extremely difficult. Cases have been reported [12] where the characteristic albumino-cytologic dissociation was present in definitely proved post-diphtheritic polyneuritis, the diagnosis being established by isolation of the *C. diphtheriae* from some innocuous cutaneous ulcer.

The recent military experiences further showed that atypical diphtheria was worldwide. Cutaneous diphtheria with subsequent post-diphtheritic neurological changes was observed in the Middle East,[14] Germany,[15] the South Pacific,[16] and India.[17] One of the authors observed an outbreak of diphtheria in Alaska where four cases of "Vincent's pharyngitis" subsequently turned out to be diphtheria and were not recognized until paralysis of accommodation and radiculoneuritis had developed.

In these atypical cases the mildness of the nasopharyngitis is quite striking. Perhaps it is the very mildness which accounts for the high incidence of the neuritis; that is, many cases are so mild that they arouse no suspicion, no cultures are taken, and the patient is not treated for diphtheria.

Cutaneous diphtheria is associated with neuritic symptoms in a high percentage of cases. Cameron and Muir [14] reported 12 cases of paralysis in 66 cases observed. Wilson [18] states that the incidence of neurological complications in diphtheria varies from 6 to 66 per cent. In general, 10 per cent of cases develop polyneuritis or some neurological complication.

The cases to be presented are interesting because they represent two separate instances in which the Guillain-Barré syndrome was not due to a preceding infection.

Case Reports

The first case is that of a 53 year old white male, a foundry worker of Italian extraction who was first seen on June 13, 1946 for weakness in both legs. The patient had been ill with pneumonia seven weeks before, had received sulfonamides and had made an uneventful recovery save for a chronic, mildly productive cough. No hemoptysis or chest pain was reported.

About two weeks after recovery from the pneumonia, the patient noticed numbness in the right hand and forearm and shortly thereafter the affected portions became weak. This condition remained stationary during the next five weeks. Five days before being seen by us, while enjoying a sunbath, the patient developed numbness in the right thigh, rapidly followed by weakness of both lower extremities. No paresthesias, headache or other neurological manifestations were present. The patient had been constipated for the past four days and had had difficulty of urination for the preceding 24 hours.

The physical examination revealed a middle-aged white male, not in acute distress. The temperature was 100°, the pulse rate 80, the respiratory rate 20, the blood pressure 106/64 mm. Hg. The pupils were equal and round, and reacted well to light and accommodation. The extra-ocular movements were normal, the sclerae and conjunctivae were clear. The fundi revealed a suggestion of bitemporal pallor. Ears, nose and throat were negative. The neck revealed marked rigidity. No masses were palpated. The thyroid gland was not palpable. There were no dilated neck veins. The lungs revealed dullness at the right base and in the left infra-clavicular area, with diminished breath sounds and voice sounds over the latter. A few coarse rhonchi were heard in both lungs. The heart was normal in size, rate and rhythm. No murmurs were heard. The abdomen revealed a distended bladder. No other viscera were palpable. The extremities were normal. The neurological examination revealed no involvement of the cranial nerves. Marked motor weakness of both lower extremities and the right forearm and hand was present. The sensory examination was normal. The ankle jerks were hyperactive, the abdominal reflexes

absent, the cremasteric reflexes sluggish. No pathological reflexes were found. The remainder of the neurological examination was normal.

The patient was admitted to St. Peter's Hospital the same afternoon, and a lumbar puncture was performed. Clear, colorless fluid was obtained under 135 mm. of water pressure. There was a negative Queckenstedt test. The total protein was 100 mg. per cent and the cell count was 3, all lymphocytes. Spinal fluid sugar was 90 mg. per cent, chlorides 660 mg. per cent. The gold curve was of the tabetic type. The Wassermann test was negative. Urine and blood count were within normal limits.

On the basis of the history, the physical findings and the spinal fluid picture, a diagnosis of infectious polyneuritis, or Guillain-Barré syndrome, was made. The lesion in the chest was thought to be an unresolved pneumonia which had precipitated the neurologic pattern. However, an x-ray of the chest on the day of admission was reported as "revealing evidence of a smooth, clear-cut, well-defined lesion extending from the mediastinum toward the central lung field on the left." The possibility of a lung tumor or aneurysm was mentioned. The patient was fluoroscoped and the mass was found to be non-pulsating and seemed independent of the aorta; therefore, the diagnosis of aneurysm was abandoned.

The course in the hospital was rapidly downward. Another spinal puncture four days after admission and the day before death again revealed 100 mg. per cent protein and 9 cells. On June 15, the patient revealed evidence of hypesthesias below the level of D–8 or 9 and the reflexes in the lower extremities became markedly diminished. The next day these signs became more marked and the cough which had developed was noticeably weaker. There was a definite level at D–6 to 7 with involvement of the muscles of respiration. The patient was placed in a respirator but the temperature climbed to 107° and the patient died by respiratory paralysis on June 17, 1946, four days after admission.

Reëxamination by the consulting neurologist shortly after admission had confirmed the findings of the Guillain-Barré syndrome and he had suggested the possibility of metastases from a lung tumor as the cause.

We realized we were dealing with the possibility of a tumor of the lung but the history of "pneumonia," the character of onset, the ascending paralysis and the spinal fluid findings made us favor an infectious basis. An x-ray of the spine was taken to disclose metastases to the vertebrae which might, by compression, produce motor and sensory level at D–6 or 7, but none was found.

At necropsy, the essential findings were: an anaplastic bronchogenic carcinoma originating in the mid-portion of the left upper lobe, spreading into the lung parenchyma, involving the lateral wall of the left auricle and one of the pulmonary veins. There were metastases to the regional lymph nodes as well as to the liver and both adrenals. The spinal cord was found to be compressed by diffuse metastases to the extradural fat infiltrating the ganglia and spinal nerve roots, extending from C–7 to D–8. Microscopic section of the nerve roots revealed extensive damage to the axis cylinders ranging from patchy degeneration to complete disappearance in some sections. The essential pathogenesis, therefore, consisted of extradural compression of the spinal cord and nerve roots from metastases within the epidural fat.

Here, then, is a patient with the Guillain-Barré syndrome who had a bronchogenic carcinoma with metastases compressing the spinal cord and nerve roots as the basic cause of the neuropathy. On perusal of the literature, two similar cases were found. One was a case of meningeal carcinomatosis in a 65-year old woman who had marked carcinomatous infiltrations around the spinal cord.[19] No primary tumor could be demon-

strated. In this case the tumor had not invaded the spinal cord proper but had enclosed the nerve roots, partially penetrating into the endoneurium of the nerve bundles. There was no evidence of degeneration of any of the tracts running in the spinal cord.

Another case of metastatic carcinoma simulating the Guillain-Barré syndrome was reported from the University of Maryland School of Medicine.[20] This case was a 40 year old white female who complained of eye symptoms and headaches following an attack of grippe and then developed weakness of the arms and legs with some bladder symptoms. She was thought to have an infectious polyneuritis but at necropsy a metastatic carcinoma involving the brain was found. There were also metastases along the vertebral column which were encroaching upon the nerve roots and the cord. These three cases are quite adequate illustrations of the importance of carcinoma as an etiologic factor in the production of the Guillain-Barré syndrome.

The second case to be presented is that of a 33 year old white male, an instructor in dramatic art at the New Jersey College for Women of Rutgers University, who was first seen on October 11, 1947 because of chills, fever and weakness. The patient had received a mild laceration of his left palm on October 8 while building a prop for a play. He was given first aid and an injection of 1,500 units of tetanus antitoxin. Late that same evening the patient developed malaise and fever. The wound was redressed the following day and appeared to be clean, but the chills, fever and malaise continued, so that on October 11 he was first seen by one of us.

Examination at that time revealed no abnormal physical findings save for some sonorous rhonchi in the lungs. That same evening the patient developed a diffuse urticaria which lasted for 24 hours and responded to pyribenzamine and propadrine. Despite symptomatic treatment the malaise and fever continued. On October 14 the patient complained of severe generalized weakness and was admitted to St. Peter's Hospital for further study. The past history was entirely uneventful except that the patient had experienced a severe reaction following immunization during his military service.

The examination on admission revealed a young white male in no apparent distress. The temperature was 102°, the pulse rate 86, the respirations 20, the blood pressure 120/76 mm. Hg. The head was normal. The eyes revealed the pupils to be equal and regular, reacting well to light and accommodation; the extra-ocular movements were normal. There was some congestion of the conjunctivae; the fundi were negative. Moderate congestion of the nose and pharynx was present. The neck revealed no definite rigidity but there was some resistance to the extremes of flexion; no nodes were palpable. The lungs revealed generalized sibilant and sonorous râles. The heart was normal in size, rate and rhythm; no murmurs were heard. The abdomen was soft, with no masses or viscera palpable. The extremities were normal. The neurological examination on admission was completely normal.

Laboratory studies revealed hemoglobin 89 per cent, erythrocytes 5,200,000; leukocytes 12,900 with 59 per cent polymorphonuclears and 31 per cent lymphocytes. The urine showed a trace of albumin, no sugar or acetone, and an occasional leukocyte.

The opinion on admission was that we were dealing with an accelerated form of serum sickness although an independent virus infection had to be considered, such as lymphocytic meningitis or infectious mononucleosis.

The patient was placed on Empirin and Pyribenzamine. After 48 hours, his temperature returned to normal and remained so throughout the remainder of his illness. The malaise and weakness persisted, however, and the nuchal rigidity increased. A spinal puncture, performed on October 16, was reported normal for protein and sugar, with a cell count of 7. On the same day the patient began complaining of extreme weakness and paresthesias of the fingers and toes. A careful neurological examination was again normal, but on the following day a diminution of the knee and ankle jerks was noted, all other reflexes being normal. By October 19 the patient had developed almost complete loss of motor power in both lower extremities with absence of knee and ankle reflexes. There was a slight sensory loss in the lower extremities as well as diminution of the position sense of the toes of the right foot. The patient also complained of paresthesias in both hands. At this time the diagnosis of a diffuse myeloradiculoneuritis—Guillain-Barré syndrome—was made and another spinal puncture was performed, which this time revealed 100 mg. per cent of protein and 1 cell, the typical albumino-cytologic dissociation.

From here on the picture developed in usual fashion with paresthesias of the hands followed in 24 hours by marked motor weakness of both upper extremities and loss of other reflexes. Weakness of the intercostal muscles developed and a respirator was kept in readiness but, fortunately, the patient's condition never reached the point for its use.

By October 22, the patient had developed complete quadriplegia and also noticed numbness of the left cheek and face. This was followed 24 hours later by a complete facial diplegia. No other cranial nerves were involved although for a time he evinced some difficulty in deglutition as well as aspiration of liquids into the trachea.

At the height of the process, the patient presented quadriplegia, facial diplegia, loss of all deep and superficial reflexes, generalized hyperesthesias and marked tenderness over the peripheral nerve trunks, chiefly of the lower extremities. Disturbances in vibratory and position sense were noted as well. The involvement of the intercostal muscles was of a peripheral type, not involving medullary centers.

After a period of one week the patient began to improve gradually in strength in the lower extremities and after several weeks he showed return of motor power so that today he is, for practical purposes, well, save for a slight residual facial weakness on the right and some minor changes of the position and vibratory senses in his right foot.

The treatment was intensive, all known modalities being tried—thiamine in large doses, Prostigmine, ephedrine, Pyribenzamine, etc., but none had any decisive effect upon the course of the disease. Intensive physiotherapy was started very early and it is our belief that this helped greatly in shortening the convalescent phase of the illness.

In this patient the question of etiology is of particular interest. In the absence of any preceding illness and in view of the relation of the onset to the administration of antitoxin, it was felt at first that this patient presented a severe serum sickness with central nervous system changes of the Guillain-Barré type. However, one had to consider a concomitant virus infection, especially infectious mononucleosis, whose close association with this syndrome has been noted by many authors.[6]

Accordingly, the heterophile antibody titer was examined and reported, surprisingly enough, as positive in a 1:112 dilution. However, when agglutinin absorption studies were done, and the test repeated, it was negative, thereby proving that infectious mononucleosis was not the etiologic factor

in this case. The value of the agglutinin absorption technic is important and we should like to dwell on it for a moment.

Forsmann [21] in 1911 was the first to recognize the non-specificity in antigen-antibody reactions by showing that blood from normal people could agglutinate sheep erythrocytes. Hanganutzin [22] in 1924 noted that the titer for heterophile antibody in people who had received an injection of horse serum became higher than was normally expected and Davidsohn [23] further showed that the titer became very high if the injection was followed by serum sickness. In 1932 Paul and Bonnell [24] discovered that infectious mononucleosis also produced extremely high titers of agglutinins to sheep erythrocytes, and since then this heterophile antibody reaction has been used as a more or less specific test for this disease. The high titer found in serum sickness, therefore, was confusing.

However, Davidsohn,[25] and later Stuart,[26] working on this problem, developed an agglutinin absorption technic and showed that the heterophile antibodies in infectious mononucleosis, serum sickness, and in normals do differ serologically. The present concept, therefore, is that there are three distinct types of sheep cell agglutinins—those in normal serum absorbed by guinea pig kidney but not beef erythrocytes; those in infectious mononucleosis absorbed by beef erythrocytes but not guinea pig kidney; and those in serum sickness, absorbed by both guinea pig kidney and beef erythrocytes. Therefore, it is possible by agglutinin absorption tests to differentiate these clinical pictures.

The value of this procedure has been amply demonstrated in large series of cases both here [27] and abroad.[28] In our case the heterophile titer was 1 : 112 when done without the absorption technic; but following the guinea pig absorption test the titer fell to 1 : 10, strongly suggesting that the immunologic changes were due to serum sickness and not to infectious mononucleosis.

Involvement of the nervous system is not uncommon in reactions following injection of horse serum. The reported cases have consisted chiefly of brachial plexus neuritis or mononeuritis, either peripheral or cranial. However, the development of a picture as diffuse as presented here is extremely rare. From the review of the literature, only two other cases were found which could be classified as fitting the criteria of the Guillain-Barré syndrome [29, 30] and neither was as severe as the case of our patient. The rapid recovery in this patient was quite striking; this is a feature of the polyradiculitis secondary to serum reactions.

Most authors agree that the nervous system complications following horse serum administration represent an allergic response of the central nervous system to serum, with edema and congestion similar to the urticarial reactions in the skin. Hadden and Wilson [31] have pointed out that skin and nerve tissue are both ectodermal in origin and might be expected to react similarly to the same allergens.

The Guillain-Barré syndrome has been found in many different pathological states—following upper respiratory infections and in the course of constitutional diseases such as syphilis and tuberculosis, specific virus infections such as hepatitis and mononucleosis, and secondary to drugs and physical traumata such as sulfonamides and hyperthermia.

We have presented two cases, one secondary to malignancy and the other as a severe manifestation of serum sickness. The occurrence of such a definite and characteristic clinical picture as the Guillain-Barré syndrome which can develop in the wake of such diversified diseases as just mentioned, strongly suggests a common anatomic basis for the clinical picture.

In reviewing the essential pathology, there appears to be such a lesion, consisting of obstruction and compression of the nerve roots and trunks, either cranial or peripheral. In the cases described by Roseman and Aring,[9] there was marked edema of the nerve bundles and nerve roots, with marked separation of the perineurium from the funiculi and infiltration with inflammatory cells in this area, as well as swelling and beading of the axis cylinders. In the case of meningeal carcinoma reported by Floyd,[19] the tumor had not invaded the spinal cord proper but had enclosed the nerve roots, partially penetrating into the endoneurium of the nerve bundles. In the first case reported here, the same obstructive lesion in the perineural tissue of the nerve roots was present.

The problem of selective albumino-cytologic dissociation has never been adequately explained. In discussing the pathological aspects of this problem with Dr. Sylvan E. Moolten, Director of Laboratories at St. Peter's Hospital, he suggested a mechanism which might explain this peculiar phenomenon; namely, that the obstruction in the perineural spaces of the nerve roots might allow for absorption of fluid but prevent the larger protein molecules from escaping into the venous circulation, thereby causing an accumulation of protein in the spinal fluid. The literature is very deficient in the matter of localization of the point or points at which reabsorption of the spinal fluid takes place. According to the more orthodox views, the spinal fluid is secreted through the choroid plexus of the lateral ventricles, circulates through the ventricular cavities into the cisterns at the base of the brain, and thence flows into the villi and pacchionian bodies and from these structures into the dural sinuses, finally emptying into the venous circulation. As the spinal cord has no choroid plexus, its fluid is thought to be derived from the cerebral subarachnoid space and, as it possesses no dural sinuses, it has been felt that the fluid flows upward to be absorbed by the villi, pacchionian bodies and dural sinuses within the cranium. However, Hassin,[22, 23] an intense student of the problem for many years, has shown by the most careful pathologic studies that the spinal fluid is not absorbed through the villi or pacchionian bodies but through the perineural spaces of the cranial nerves and spinal nerve roots. Under normal conditions, there occurs a re-absorption of spinal fluid and its contents through these perineural spaces.

However, when these spaces are blocked by allergic edema, inflammatory reaction, or malignant metastases, there still may be absorption of fluid, but no absorption of the larger protein molecules. This would account for the large amount of protein being present in the lumbar puncture fluid. As there is no meningeal involvement, no tendency to pleocytosis is encountered.

Aring [34] has done important studies on comparative protein levels in the lumbar area and the cisterna magna in cases of the Guillain-Barré syndrome. He found that normal levels were present in the cisternal puncture fluid, whereas abnormal levels were found in the lumbar puncture fluid. It may be that cases with cranial nerve involvement may have high cisternal levels as well.

In conclusion, therefore, we should like to emphasize the obstructive radiculopathy which seems to account for the majority of nerve root phenomena, both cranial and peripheral, and the spinal fluid findings which have been such a characteristic feature of this ill-defined, yet common syndrome.

Summary

1. Two cases of the Guillain-Barré syndrome are presented.

2. These cases are unusual in that they do not represent post-infectious phenomena.

3. One case was due to bronchogenic carcinoma with metastases to the extradural fat compressing the spinal cord and nerve roots from C–7 to D–8.

4. The second case represents an unusual form of serum sickness following tetanus antitoxin injection. This case showed most extensive neurological involvement with rapid and practically complete recovery.

5. The usefulness of the agglutinin absorption technic in interpreting heterophile antibody titers was amply demonstrated. By this means it was possible clearly to differentiate serum sickness from infectious mononucleosis.

6. A common anatomic basis for the Guillain-Barré syndrome, regardless of the etiology, is suggested. It is believed that the basic pathologic process consists of an obstruction to the perineural circulation of the cerebrospinal fluid as the nerve roots emerge from the cord, permitting absorption of fluid and electrolytes but preventing the absorption of the larger protein molecules. Thus the characteristic albumino-cytologic dissociation may be explained.

BIBLIOGRAPHY

1. Osler, W.: The principles and practice of medicine, 1892, Appleton, New York.

2. Patrick, H. T.: Facial diplegia in multiple neuritis, J. Nerv. and Ment. Dis. **44**: 322–333, 1916.

3. Guillain, G., Barré, J. A., and Strohl, A.: Sur un syndrome de radiculonévrité avec hyperalbuminose du liquide céphalorachidien sans réaction cellulaire. Remarque sur les caractères et graphiques des réflexes tendineux, Bull. et mém. de Soc. méd. des hôp. d. Paris, **40**: 1462, 1916.

4. Bradford, J. R., Bashford, E. F., and Wilson, J. A.: Acute infective polyneuritis, Quart. J. Med. **12**: 88–126, 1918.
5. Casamajor, L.: Acute ascending paralysis among troops; pathologic findings, Arch. Neurol. and Psychiat. **2**: 605–620, 1919.
6. Hiller, R. I., and Fox, M. J.: Infectious neuronitis associated with infectious mononucleosis, Marquette M. Rev. **7**: 152–154, 1943.
7. Guillain, G.: Radiculoneuritis with acellular hyperalbuminosis of the cerebrospinal fluid, Arch. Neurol. and Psychiat. **36**: 975–990, 1936.
8. Gilpin, S. F., Moersch, F. P., and Kernohan, J .W.: Polyneuritis: a clinical and pathological study of a special group of cases frequently referred to as instances of neuronitis, Arch. Neurol. and Psychiat. **35**: 937–963, 1936.
9. Roseman, E., and Aring, C. D.: Infectious polyneuritis: infectious neuronitis, acute polyneuritis with facial diplegia, Guillain-Barré syndrome, Landry's paralysis, etc., Medicine **20**: 463–494, 1941.
10. Forster, F. M., Brown, Madelaine, and Merritt, H. H.: Polyneuritis with facial diplegia, New England J. Med. **225**: 51–56, 1941.
11. McIntyre, H. D.: Infective neuronitis, Ohio State M. J. **33**: 875–883, 1937.
12. Delp, M. H., Sutherland, G. P., and Hashinger, E. H.: Post-diphtheritic polyneuritis: a report of five cases with albumino-cytologic dissociation simulating the Guillain-Barré syndrome, Ann. Int. Med. **24**: 618–628, 1946.
13. Liebow, A. A., MacLean, P. D., Bumstead, J. H., and Welt, L. G.: Tropical ulcer and cutaneous diphtheria, Arch. Int. Med. **78**: 255–295, 1946.
14. Cameron, J. D. S., and Muir, E. G.: Cutaneous diphtheria in Northern Palestine, Lancet **2**: 720–723, 1942.
15. Weigmann, F.: Bakteriologische Untersuchungen über Wund diphtherie, Bull. Hyg. **18**: 763, 1943.
16. Norris, R. F., Kern, R. A., Schenck, H. P., and Silcox, L. E.: Diphtheria in the tropics: a report of 18 cases on a United States naval hospital ship, U. S. Nav. M. Bull. **42**: 518–524, 1944.
17. Bumstead, H. J.: A limited outbreak of diphtheria exhibiting both cutaneous and faucial lesions, J. Roy. Army M. Corps **67**: 295–307, 1936.
18. Wilson, S. A. K.: Neurology, 1940, Williams & Wilkins Co., Baltimore.
19. Floyd, H. S.: Meningeal carcinomatosis simulating the clinical syndrome of polyradiculoneuritis, Bull. Charlotte (N. C.) Mem. Hosp. **1**: 34–39, 1944.
20. Guyther, J. R.: A case of metastatic carcinoma simulating the Guillain-Barré syndrome, Bull. School Med., Univ. Md. **30**: 84–90, 1945.
21. Forsmann, J.: Die Herstellung nacht vertiger spezifischer Schafhämolysme ohne Verwendung von Schlafblüt, Biochem. Ztschr. **37**: 78, 1911.
22. Hanganutzin, M.: Hémagglutinines hétérogénétiques après injections de sérum de chaval, Compt.-rend. Soc. de biol. **2**: 1457, 1924.
23. Davidsohn, I.: Heterophile antigens and antibodies, Arch. Path. and Lab. Med. **4**: 776, 1927.
24. Paul, J. R., and Bonnell, W. W.: The presence of heterophile antibodies in infectious mononucleosis, Am. J. M. Sc. **183**: 90, 1932.
25. Davidsohn, I.: Heterophile antibodies in serum disease, third report, J. Infect. Dis. **53**: 219, 1933.
26. Stuart, C. A., Burgess, A. M., Lawson, H. A., and Wellman, H. E.: Some cytologic and serologic aspects of infectious mononucleosis, Arch. Int. Med. **54**: 199–214, 1934.
27. Kaufman, R. E.: Heterophile reaction in infectious mononucleosis, Ann. Int. Med. **21**: 230–251, 1944.
28. Dempster, G.: Some serological aspects of infectious mononucleosis with special reference to use of agglutinin-absorption tests in diagnosis, Edinburgh M. J. **53**: 296–310, 1946.

29. Kamman, G. R., and Weisberg, M.: Polyneuritis with facial diplegia following serum sickness in an adult, Minnesota Med. **23**: 789–791, 1940.
30. Coogan, T. J., Martinson, D. L., and Mathews, W. H.: Neurological symptoms of infectious mononucleosis, Illinois M. J. **57**: 296–302, 1945.
31. Wilson, George and Hadden, S. B.: Neuritis and multiple neuritis following serum therapy, J. A. M. A. **98**: 123–125, 1932.
32. Hassin, G. B.: Cerebrospinal fluid pathways (critical note), J. Neuropath. and Exper. Neurol. **6**: 172–177, 1947.
33. Hassin, G. B.: Cerebrospinal fluid: its origin, nature and function, J. Neuropath. and Exper. Neurol. **7**: 172–182, 1948.
34. Aring, C. D.: Infectious polyneuritis, Clinics **4**: 263–274, 1945.

ACUTE PERICARDITIS: A REPORT OF EIGHT CASES IN WHICH THE ETIOLOGY WAS "NON-SPECIFIC" OR "CRYPTIC" *

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Acute pericarditis usually occurs in the presence of more or less easily recognized infections elsewhere in the body, as with rheumatic fever, pneumococcic pneumonia, septicemia or tuberculosis, to mention the more common examples. That it may occur spontaneously and without the demonstration of any known infectious agent is not well known. Such cases have been called acute, non-specific pericarditis. The sudden onset and the severity of the chest pain may be such as to lead to the erroneous diagnosis of coronary thrombosis,[1, 2, 3] or to pulmonary infarction.[4]

The recognition of several cases of acute, primary or non-specific pericarditis in the Albany Hospital led to the realization that this condition was not generally appreciated as a clinical entity, at least in this locality. Accordingly this study was undertaken.

Table I

Etiology	Number of Patients
Tuberculosis, pulmonary	5
Rheumatic fever	1
Respiratory infection	6
Pharyngitis	2
Pneumonia	4
Uremia	1
Post-operative	1
Non-specific	3
Cryptic	3

The 11,674 electrocardiograms which had been taken in the Albany Hospital from 1936 to 1946 were reviewed. Acute pericarditis was diagnosed in 15 cases. Since then five more have been added for a total of 20 cases. In table 1 these are tabulated as to etiology and it can be seen that 13 were due to generally known factors as pulmonary tuberculosis, respiratory infection, uremia and rheumatic fever. In three cases the cause of the pericarditis was unknown (so-called "non-specific") and in three the etiology was cryptic but the pericarditis was associated with and probably due to such diverse things as hemochromatosis, infected hemorrhoids and vaccination. In addition to the three cases of non-specific pericarditis and the three of obscure but known etiology, two other cases are reported because of the unusual onset. These were associated with respiratory infections.

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Case Reports

Case 1. A 55 year old machinist was feeling perfectly well until one morning at 1:30 a.m. when he rose from bed to go to the bathroom and was suddenly stricken with substernal pain, sharp, squeezing and excruciating in nature. He soon became very dyspneic. He was taken to his doctor's office where he received 100 mg. of Demerol at 2:35 a.m. and again at 3:00 a.m. His pain decreased somewhat but his blood pressure fell to 90 mm. Hg systolic and 60 mm. diastolic. He was admitted to the hospital at 4:00 a.m. complaining of substernal pain and suffocation. His temperature was 97.8°, pulse 82 and respirations 24. He was dyspneic, orthopneic, cyanotic. It was necessary to give him morphine and oxygen.

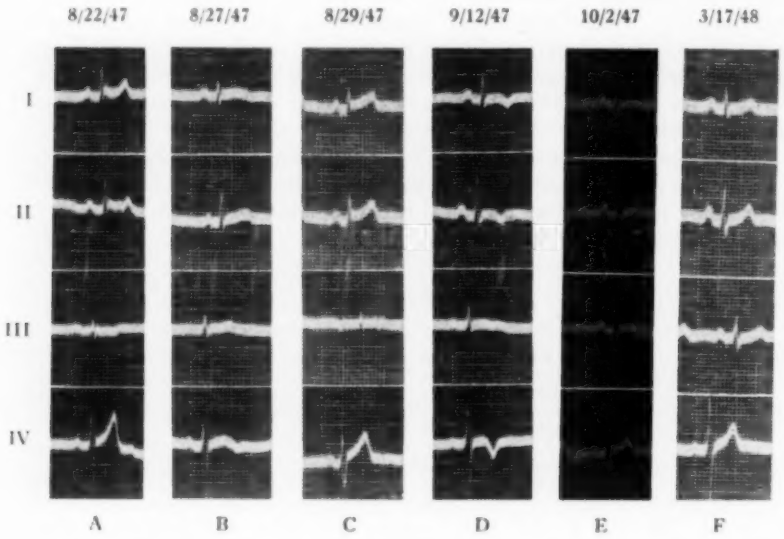

Fig. 1. (*Case 1*). Electrocardiograms taken on the first, fifth, seventh, twenty-first and forty-first days of illness. A: Note slight elevation of $ST_{1,2,4}$. B: $ST_{1,2,4}$ are lower and $T_{1,2,4}$ are lower. C: (taken during a recurrence of symptoms) $ST_{1,2,4}$ elevated again and $T_{1,2,4}$ taller. D: Note lowering of ST and inversion of T in I, II, IV. E: Normal except for low T_1. F: (seven months after onset of illness) normal tracing taken on follow-up.

Examination showed the heart to be of normal size, the rhythm regular, the sounds distant and of fair quality. There were no murmurs. There were râles at both lung bases. The upper abdomen was slightly rigid. The white blood count was 10,100 with 88 per cent polymorphonuclear leukocytes. On the third hospital day a pericardial friction rub was noted and this persisted for 17 days. He improved rapidly, but on the seventh day had another attack of severe precordial pain which required the use of morphine and oxygen again. The pain gradually subsided over the course of the next five days and from then on his convalescence was uneventful. His temperature became normal on the fourteenth day and remained so except for an occasional unexplained rise to 99.6°. A roentgen-ray of the chest taken on the twentieth day of illness showed the heart to be normal in size.

Serial electrocardiograms supported a diagnosis of acute pericarditis (figure 1). They were taken on the first, fifth, seventh, twenty-first and forty-first days of illness. The first (1–A) showed upright T-waves in Leads I, II and IV, with slightly high origin. The second (1–B) showed a lowering of the ST segments and of the T-waves in these leads. The third (1–C), which was taken during a recurrence of pain and dyspnea, revealed that $T_{1,2,4}$ were upright again with elevation of the ST segments, suggesting a reactivation of the pericarditis. The next record (1–D) showed further evolution of the process with inversion of $T_{1,2,4}$ and some lowering of $ST_{1,2,4}$. The last record taken during the illness showed a return to normal with the exception of a low T_1 (1–E).

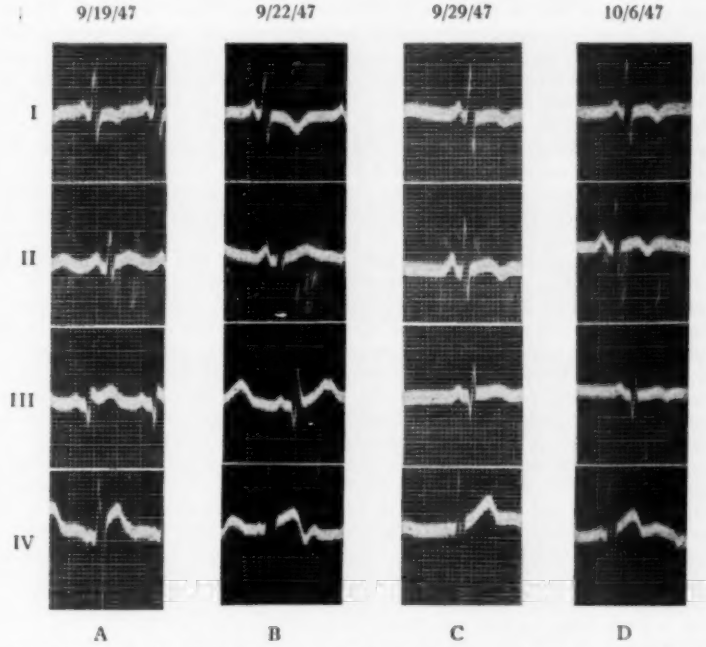

FIG. 2. (*Case 2*). Electrocardiograms taken on the second, fifth, ninth and sixteenth hospital days. A: Observe depression of ST_1 and inversion of T_1; $ST_{2,3,4}$ are elevated. B: ST_1 is lower and T_1 more inverted; $ST_{2,3,4}$ are lower and T_4 is inverted. C: T_2 is now inverted; T_3 is lower and T_4 is upright. D: T_2 is now inverted and T_4 shows late inversion.

A follow-up on this patient seven months after the onset of illness revealed that he had mild dyspnea on bending over and on exertion. He stated that ever since the attack respirations seemed to be short and rapid. He has also had occasional, mild "kinky" pain over the heart which is not related to exertion. He has noted a sensation of "butterflies" in the chest, at times. Examination of the heart was normal except for a rare premature beat and the blood pressure was 150 mm. Hg systolic and 100 diastolic. The electrocardiogram was normal at this time (figure 1–F).

Case 2. A 23 year old tree sprayer awoke one morning with upper abdominal pain, dull and constant, just below the xiphoid. He went to work, however, and took

various antacids without relief of the pain. He perspired profusely that day and night and complained of headache. The following day, he saw his doctor who found his temperature was 104° and his white blood count was 20,000. He was admitted to the hospital on the third day of his illness where his temperature was recorded as 100°, pulse 80 and respirations 30, blood pressure 130 mm. Hg systolic and 80 diastolic. He was a dyspneic, pale, distressed-looking man. Except for an apical systolic heart murmur and slight enlargement of the liver, the examination revealed nothing. His white blood count was 27,100 with 88 per cent polymorphonuclear leukocytes. On the second day, a to and fro pericardial friction rub was heard. The patient complained of pain on deep inspiration and on slight motion of the trunk. He sweated copiously. His blood pressure dropped to 88 mm. Hg systolic and 72 diastolic. Penicillin was given but his temperature remained elevated between 99 and 100° for the first four days of hospitalization before becoming normal. Coincident with normal temperature was the disappearance of the pain except for an occasional sharp jab over the precordium on deep breathing. His white blood count at this time was 13,800 and on the thirteenth day was normal. The friction rub lasted for seven days.

Figure 2 shows the electrocardiograms obtained. They were consistent with acute pericarditis. They were taken on the second, fifth, ninth and sixteenth hospital days. The first record (2–A) showed depression of ST_1 with T_1 inverted; $ST_{2,3,4}$ were elevated. The second record (2–B) showed T_1 more inverted, R_3 had appeared, T_3 was more prominent and T_4 was inverted. On the ninth day (2–C) T_1 was less inverted, T_2 had become inverted and T_3 showed late inversion. The last record (2–D) showed the process was not yet stabilized, T_3 being inverted and T_4 showing late inversion. A follow-up could not be obtained on this patient.

Case 3. A man of 28 years was well until four months before admission when he developed sudden chest pain and shortness of breath while exercising. He saw many physicians who could find nothing wrong and during the course of the next two months, the pain disappeared. He was then well until four days before admission when he complained of substernal pain increased by inspiration. The pain became more severe and radiated to the left shoulder. For two days and nights before admission the pain was very severe and required morphine for relief.

On entering the hospital, his temperature was 98.6°, pulse 132, and respirations 34; blood pressure 108 mm. Hg systolic and 70 mm. diastolic. Physical examination showed only dyspnea and orthopnea. The white blood count was 15,600. Later that day, he developed severe substernal pain, knife-like in character, for which he was given morphine gr. ¼ q. 3 h. He also received oxygen for labored breathing and cyanosis. Another attack was noted the next day and this time the nurse reported she was unable to obtain the patient's pulse or blood pressure. On the fourth hospital day a pericardial friction rub was heard, disappearing within about 24 hours. A chest roentgen-ray revealed the presence of a small pleural effusion and enlargement of the heart probably due to a pericardial effusion. The temperature remained between 103 and 104° until the fifth day when it returned to normal. It rose again on the tenth hospital day reaching 102° or 103° intermittently until the twentieth day when it dropped and remained normal until discharge. During this time he continued to have low-grade substernal pain, especially on exertion, so that he was afraid to move in bed. He was discharged with roentgent-ray signs of a small pleural effusion and cardiac enlargement after seven weeks in the hospital.

He was readmitted two months later for further treatment. He had been in bed since discharge except for two hours daily. He reported he had had slight substernal pain on deep inspiration and a sensation of fluid in the chest on sudden movement. After three weeks at home without signs of fever, his temperature rose to 103° and there was an exacerbation of pain which spread across his entire chest anteriorly and radiated to the right scapula. The fever lasted five days and then the pain gradually subsided. Since then, he had been dyspneic and increasingly conscious of splashing

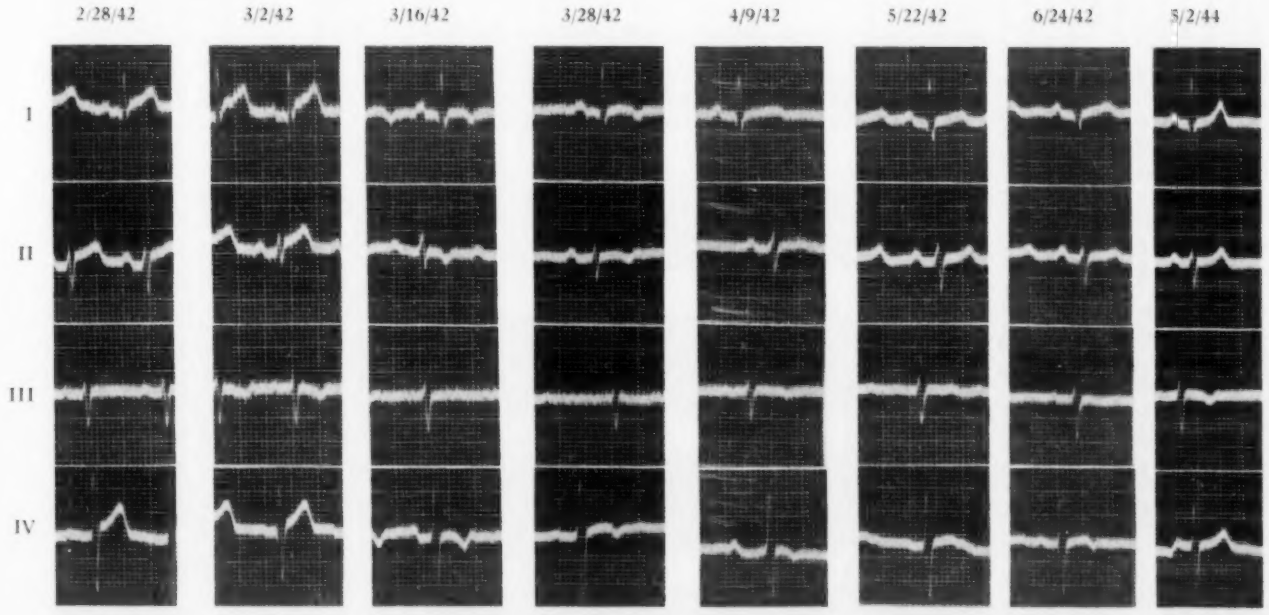

FIG. 3. (*Case 3*). A: (First hospital day) Note elevation of $ST_{1,2,4}$. B: (Third day) Further elevation of $ST_{1,2,4}$; $T_{1,2}$ are taller; T_3 is inverted. C: (Nineteenth day) ST segments are isoelectric and $T_{1,2,4}$ are now inverted. D: (Thirty-first day) There is little change from the previous record. E: (Forty-third day) Improvement beginning to occur, with T_3 becoming upright but with a tendency to late inversion and T_2 upright though small. F: (Three months) Continued improvement can be seen in $T_{1,2}$. G: (Four months) T_4 partially inverted. H: (Two years later) Normal record, except for left axis deviation.

in the chest. Thoracentesis yielded 400 c.c. of serosanguinous fluid which was negative for tubercle bacilli on direct smear and on guinea pig inoculation.

Figure 3 shows the electrocardiograms taken on this patient. The first electrocardiogram (3–A) taken on the first day of hospitalization, showed a rapid pacemaker rate of 104, left axis deviation suggesting some left ventricular enlargement, and elevation of $ST_{1,2,4}$. On the third day (3–B) there was further elevation of $ST_{1,2,4}$; $T_{1,2}$ were taller; T_3 was inverted. On the nineteenth hospital day (3–C) the ST segments had become isoelectric and there was sharp inversion of $T_{1,2,4}$. The ascending limb of these T-waves was concave upward. On the thirty-first day (3–D) the rate had slowed to 68 and T_4 was not as deeply inverted. Otherwise, there was little change. On the forty-third hospital day (3–E) T_1 was mainly upright with a tendency to late inversion; T_2 was mainly upright and small; T_3 was slightly inverted and T_4 remained the same as before. These changes in $T_{1,2}$ were interpreted as showing some improvement. The next electrocardiogram was taken on the second admission (3–F) almost three months after the first record, and showed $T_{1,2}$ to be upright and slightly taller than previously; T_3 was flat or slightly upright and T_4 was low and notched. One month later (3–G) T_3 was again flat or slightly inverted, T_4 partially inverted. The last record (3–H), taken about two years later, was within normal limits except for left axis deviation.

Personal interview with this patient could not be arranged.

In the three cases detailed above, the etiology of the infection is obscure and unknown; they may properly be called examples of non-specific pericarditis. In the next three cases the etiology is cryptic but the pericarditis was associated with a disease process elsewhere in the body and probably due to it.

Case 4. A 38 year old chemist was admitted to the hospital complaining of severe substernal and right anterior chest pain radiating to the right shoulder and right posterior chest, onset 12 hours before. It was aggravated by deep breathing and associated with a fever of 102° and sweating. There was also generalized aching but no cough or cold. A chest roentgen-ray taken before admission was reported negative. His past history revealed that he had occupational contact with hepatotoxic chemicals five years previously. For a few months prior to admission, occasional epistaxis, nausea and light-colored stools had been noted.

His temperature was 102°, pulse 88, respirations 19 and blood pressure 84 mm. Hg systolic and 50 diastolic. He appeared acutely ill. The pharynx was diffusely injected. The heart seemed normal. There was moderate icterus and the liver was enlarged four fingers'-breadth below the costal margin, the edge sharp, non-tender and irregular. On the second day, a pericardial friction rub was heard. This lasted for 24 hours at which time the temperature was normal. The pain was controlled with codeine and aspirin. A chest roentgen-ray taken on the third day did not show any cardiac enlargement.

The urine was normal. Hemoglobin 12.5 gm.; red cell count 3,280,000; white cell count 6,500. Wassermann test negative. Nonprotein nitrogen 29 mg. per cent. Serum bilirubin 2.5 mg. per cent. Icteric index 12. Van den Bergh test positive, direct, biphasic. Blood sugar 122 mg. per cent. Serum proteins 7.1 gm. per cent with normal A/G ratio. Alkaline phosphatase 5.3 Bodansky units. Phosphorus 3.8 mg. per cent. Cholesterol 116 mg. per cent and cholesterol ester 73 mg. per cent. Coagulation time and bleeding time normal. Red blood cell fragility normal. Stool grossly normal.

An electrocardiogram taken at this time is shown in figure 4–A where $ST_{1,2}$ are elevated. Two days later (4–B), $ST_{1,2}$ are elevated and $T_{1,2,4}$ are lower.

The patient remained well for seven months until he awoke one night with severe precordial pain. Rest in bed was required for 10 days and codeine was given for pain. About two months following this he had slight precordial pain on breathing and was in bed for four days. Figure 4–C and 4–D show the electrocardiograms taken at this time.

He has remained without any further recurrence of pain until the present. In the meantime, investigation has resulted in a diagnosis of hemochromatosis. It is quite possible that the deposition of hemosiderin in the heart and pericardium caused the attacks of pericarditis. An electrocardiogram (figure 4–E), taken about three

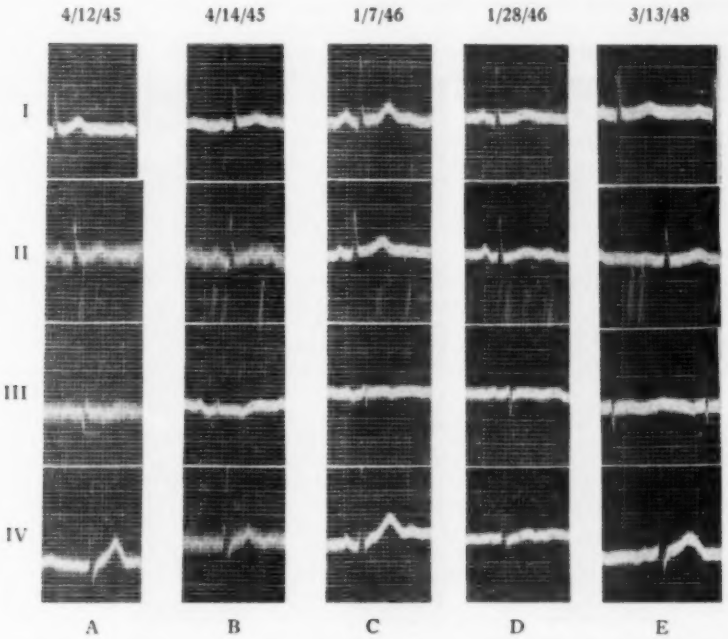

FIG. 4. (*Case 4*). A: Note elevation of $ST_{1,3}$. B: $ST_{1,3}$ remain elevated and $T_{1,2,4}$ are lower. C: (Taken during a reactivation of pericarditis) $ST_{1,2,4}$ are elevated. D: (Three weeks later) ST segments and T-waves are lower. E: (Three years after onset of illness) Normal tracing except for slight left axis deviation.

years after the onset of the first attack of pericarditis is normal except for slight left axis deviation. Examination of the patient reveals an essentially normal heart. He is still jaundiced and the liver remains enlarged.

Case 5. A 49 year old coal dealer consulted his local doctor about three weeks before admission because of fairly severe pain in the upper back and beneath the clavicles bilaterally. At this time he was also having trouble with painful, prolapsed hemorrhoids. About two weeks before admission he noted increasing dyspnea which became so marked that he could hardly talk on the telephone and two days before admission he began to complain of precordial pain. His temperature was 102° and his pulse was 96. The next day a pericardial friction rub was heard at the apex. He

complained of a dull ache over the precordium interrupted by intermittent sharp, knife-like pains over the heart, sometimes shooting to the back beneath the scapula and worse with movement. His temperature then was 104° and sulfadiazine was started. On the following day, the area of cardiac dullness seemed to be increased and the patient was sent to the hospital.

On arrival, the temperature was 103°, pulse 88, respirations 24 and blood pressure 110 mm. Hg systolic and 65 diastolic. The heart was enlarged to percussion 2 cm. beyond the midclavicular line. There was a loud systolic murmur over the apex and over the base of the heart was a to and fro friction rub synchronous with the heart beat. There were a few expiratory râles at the base of the left lung posteriorly. There were prolapsed, thrombosed hemorrhoids.

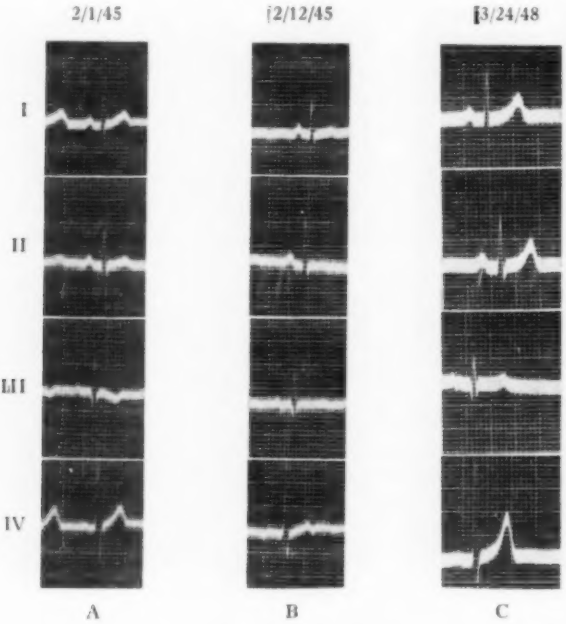

FIG. 5. (*Case 5*). A: (First hospital day) Not unusual; T_3 inverted. B: (Twelve days later) T_1 is much lower, sometimes inverted; T_2 is flatter, sometimes inverted; T_3 is flat; T_4 is much lower. C: (Three years later) Normal electrocardiogram on follow-up.

The white blood count was 8,800 with 84 per cent polymorphonuclear leukocytes and the sedimentation rate was 38 mm. per hour, corrected (Wintrobe method). Roentgen-ray showed marked cardiac enlargement with general and symmetrical accentuation of the lung markings. Blood culture was negative.

For four days, the patient's temperature fluctuated between 102 and 103° gradually dropping to normal on the twentieth day. The friction rub disappeared on the fifth day and thereafter convalescence was uneventful. On the twentieth day a hemorrhoidectomy was done under spinal anesthesia without difficulty.

Electrocardiograms taken on this patient are reproduced in figure 5. One taken on the first day (5–A) showed only an inverted T_3. Twelve days later (5–B), T_1

was much lower, sometimes inverted; T_2 was flatter and sometimes inverted; T_3 was flat and T_4 was much lower.

In the three years since the onset of his illness, the patient has been careful not to exert himself severely. He mows the lawn and shovels snow. There has never been any recurrence of pain until a few weeks ago when he pushed his car which was stuck in the snow. For one week after that he had a dull ache over the heart and under the shoulders. It was increased by movement and by walking too fast. No fever was noticed and the pain disappeared three days ago. Examination of the heart was normal. An electrocardiogram taken at this time is shown in figure 5–C. It is normal.

It is felt that the primary focus of infection in this instance was in the inflamed hemorrhoids and that a transient bacteremia may possibly have been responsible for the pericarditis. It was opportune that the follow-up examination came so soon after the patient began to complain of precordial pain subsequent to unusual exertion. The negative findings completely reassured the patient who is inclined to be heart conscious and he has been symptom free ever since.

Case 6. A grocer, aged 33, was vaccinated for smallpox 11 days before admission. Four days before admission the site became infected and increased in size. The following day he had chills and fever. The next day he developed substernal pain. His temperature was 102.4° on admission to the hospital, pulse 120, respirations 24, and blood pressure 125 mm. Hg systolic and 82 diastolic. Positive findings were limited to the site of the vaccination which was surrounded by a zone of erythema extending from shoulder to elbow. It was swollen, tender and very painful. The heart and lungs were negative on admission. The white blood count was 14,000 with 78 per cent polymorphonuclear leukocytes.

Sulfadiazine was started immediately. On the second day, the pulse rate jumped to 136 and auscultation revealed a pleuropericardial friction rub. The rub was to and fro in character, not present on inspiration but quite loud on expiration. Pain was increased by deep breathing. A chest binder gave considerable relief. The next day he complained of a dull, precordial ache. The heart seemed to be enlarged to the left and there were râles at the base of the left lung. A portable roentgenogram was suggestive of cardiac enlargement but was not considered a reliable means of measurement. The temperature fell to normal on the fourth day and remained so. A roentgenogram taken on the thirteenth hospital day showed the heart to be normal in size and revealed evidence of pleurisy in the right costophrenic angle.

Electrocardiograms taken during the hospital stay are shown in figure 6. One taken on the third day (6–A) showed elevation of $ST_{1,2,3}$; T_2 was low and T_3 inverted. On the sixth day (6–B), A–V conduction was increased but still normal; $ST_{1,3}$ remained elevated and somewhat prolonged; T_3 was still inverted. On the thirteenth day (6–C), there was less elevation of $ST_{1,3}$; T_3 had become flat or slightly upright. Two days later (6–D), $T_{1,3}$ were a little taller and the record as a whole seemed to be approaching normal.

Five years after discharge, a follow-up was made. It was found that the patient had remained in bed for one month after reaching home. He then went to work as a meat cutter lifting sides of beef weighing 150 to 180 pounds. When he was tired at night there was soreness over the precordium which lasted until one year ago when he retired from business. After a two month vacation all symptoms disappeared. He never had any symptoms referable to the heart until this winter when soreness around the heart returned after shoveling snow. At the time of the follow-up, examination was normal except for a blood pressure of 152 mm. Hg systolic and 110 diastolic. The electrocardiogram, which is shown in figure 6–E, was normal.

In this case, the source of the primary infection was apparently the infected vaccination. It is worthy of comment that both Case 5 and Case 6 were free from

any precordial pain for three years and one year, respectively, and that symptoms returned in each instance after unusual physical exertion.

Case 7. A 37 year old clerk was well until the onset of squeezing precordial pain. He soon became dyspneic and vomited. His doctor gave him morphine and papaverine and sent him to the hospital four hours after the onset of the pain.

On admission, his temperature was 100°, pulse 100, respirations 20, blood pressure 130 mm. Hg systolic and 80 diastolic. He looked acutely ill, was anxious, pale and complained of precordial and substernal pain. The heart sounds were of good quality; there was an apical systolic murmur and a to and fro friction rub could be heard. The white blood count was 23,450 with 86 per cent polymorphonuclear

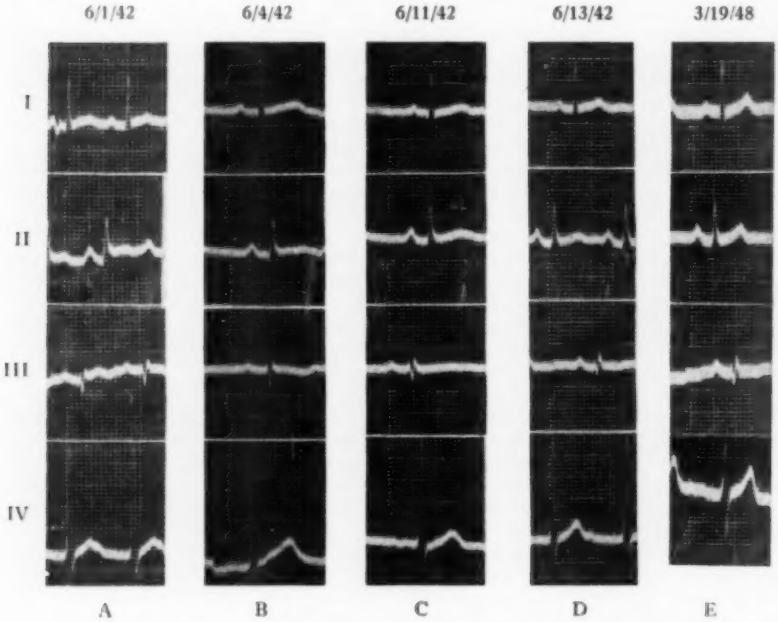

FIG. 6. (*Case 6*). A: (Third hospital day) Note elevation of $ST_{1,2,3}$; T_3 is low and T_3 inverted. B: $ST_{1,2}$ remain elevated and somewhat prolonged; T_3 is still inverted. C: There is less elevation of $ST_{1,2}$ and T_3 has become flat or slightly upright. D: $T_{1,2}$ are a little taller. E: Normal electrocardiogram obtained on follow-up.

leukocytes. The sedimentation rate was 40 mm. in one hour (Wintrobe). The friction rub disappeared the following day. On this day, the presence of an upper respiratory infection was noted. On the third hospital day, the white blood count was 9,450. The patient was comfortable and had no pain.

Serial electrocardiograms taken on this patient are shown in figure 7. The first (7–A), taken on the day of admission, revealed elevation and arching of ST in all leads; T_1 showed late inversion and T_3 was prominent. The second electrocardiogram (7–B) taken three days later, showed T_1 inverted; $T_{2,3}$, $ST_{2,3,4}$ lower and T_4 had become inverted. The third record (7–C) taken 12 days after admission, showed that T_3 had become inverted and T_4 was more inverted. Six weeks after the onset of symp-

toms (7–D) only T_4 remained inverted. Four months after the initial symptoms the electrocardiogram (7–E) was normal as was physical examination.

Although the presence of an upper respiratory infection was not noted until 24 hours after the onset of precordial pain, it probably was responsible for the development of the pericarditis. The explosive beginning of the pain simulated acute coronary occlusion to such a degree that the patient's physician favored that diagnosis for some days.

Case 8. A 63 year old farmer dated the onset of his illness two days before admission when, while out walking, he began to have precordial pain, staggering, dizziness and the feeling that everything was turning black. He felt extremely tired and went to bed where he remained until admission. The next day, there was some cough and expectoration.

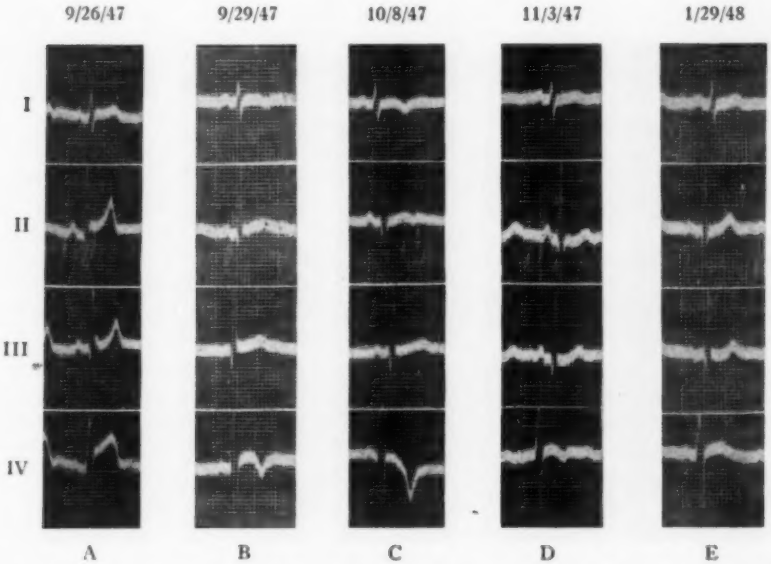

FIG. 7. (*Case 7*). A: (Day of admission) Note elevation and arching of ST in all leads. B: (Three days later) T_1 is inverted; $T_{2,3}$, $ST_{2,3,4}$ are lower and T_4 is inverted. C: (Twelve days after admission) ST segments are lower; T_2 is inverted and T_4 is more inverted. D: (Six weeks after onset) Only T_4 remains inverted. E: (Four months after onset) Normal electrocardiogram.

On arrival at the hospital, his temperature was 100°, pulse 80, respirations 20 and blood pressure 108 mm. Hg systolic and 70 diastolic. Except for a systolic murmur at the apex of the heart and a few crackling râles at the base of the right lung, the examination was not remarkable. The white blood count was 14,000 with 90 per cent polymorphonuclear leukocytes. Sedimentation rate 13 mm. per hour (Wintrobe). A roentgenogram showed the heart slightly enlarged and the lung markings accentuated, especially in the mid-portion and at the base of the left lung, consistent with a pneumonitis. The day after admission, a definite pericardial friction rub was heard, lasting for seven days. He was asymptomatic from the second day. He was treated with penicillin for the first four days and with salicylates after that.

A pleural effusion was demonstrated by a roentgenogram on the thirteenth hospital day and there was also some increase in heart size. Three days later he was discharged to the care of his local doctor.

Serial electrocardiograms supported the diagnosis of acute pericarditis. The first one (8–A) taken the day after admission, showed elevation of the ST segment in all leads with T_4 diphasic. The next one (8–B) taken three days later, showed a lowering of the T-waves in the three standard leads with depression of $ST_{2,3,4}$; T_4 had become taller and more prominent. The third electrocardiogram (8–C) taken on the fifteenth hospital day, showed that $T_{1,2,4}$ were now inverted; ST_1 was less elevated and more arched; ST_2 was arched; T_3 was low and variable and ST_4 was more depressed. The next record (8–D) taken after six weeks of hospitalization, showed T_3 was less inverted; ST_4 was less depressed and T_4 was less inverted.

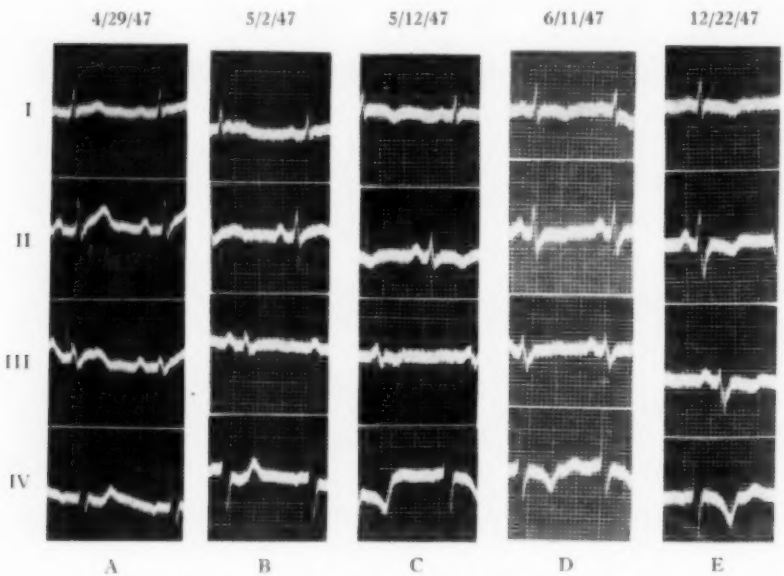

FIG. 8. (*Case 8*). A: (Second hospital day) Slight elevation of ST segment in all leads with T_4 diphasic. B: Note lowering of $T_{2,3,4}$ and depression of $ST_{2,3,4}$; T_4 is taller. C: (Fifteenth day) $T_{1,2,4}$ are now inverted; $ST_{1,2}$ are more arched; ST_4 is more depressed. D: (Six weeks) T_2 less inverted and ST_4 less depressed; T_4 less inverted. E: (Follow-up at eight months) $T_{2,4}$ are more sharply inverted indicating further myocardial damage but no acute process.

The last electrocardiogram (8–E) was taken at the time of a follow-up examination, eight months after the onset of his illness. It showed irregular rhythm due to frequent premature beats; T_2 and T_4 were more sharply inverted indicating further myocardial damage but no acute process. He stated that he was feeling well. He arises daily at 5:30 a.m. to care for 30 cows and works all day without symptoms. Examination showed the heart to be slightly enlarged to the left; the rate and sounds were normal but the rhythm was irregular due to frequent premature beats. The blood pressure was normal and so were the lungs.

The pericarditis was undoubtedly secondary to a pneumonitis but the atypical onset illustrates how easily one might confuse the precordial pain with that due to coronary thrombosis.

Comment

"Acute pericarditis is an acute inflammation of the pericardium, and the reaction in this structure is invariably an integral part of a systemic disease, a septicemia or an inflammatory extension to the pericardium from contiguous diseased tissues or organs," according to Porter.[5] Most of the cases of pericarditis can be classified thus. Occasionally, however, the etiology is not apparent. The patient may not have any obvious infection or the infection, if it is present, may be thought not to have any connection with the pericarditis. Such cases have been termed acute non-specific or acute idiopathic pericarditis. This is the type which may be mistaken for acute coronary thrombosis.[3] In most instances careful consideration of the following points will aid in the differentiation.

The pain of pericarditis is often accentuated by movement of the trunk, swallowing or breathing.[1] The friction rub, which is diagnostic when heard, often appears within a few hours in pericarditis, much sooner than with myocardial infarction.[6] The presence of fluid in the chest may indicate pleural involvement. It is doubtful that there can be pain in the absence of pleuritis. It has been pointed out that uremic pericarditis is not complicated by pleuritis and that pain is never a symptom.[5] No abnormal ventricular pulsations are seen whereas they are present in the majority of cases of infarction. Fever may be present earlier, may reach a higher level and be of longer duration than with coronary thrombosis. Acute pericarditis usually occurs in younger persons and symptoms of upper respiratory infection are more numerous than with coronary occlusion. As with some of the cases cited, however, such symptoms may be absent.

The electrocardiographic changes seen in acute pericarditis are characteristic.[1, 7] There is elevation of the ST segment in all of the standard leads as well as in Lead IV although it may occur only in Leads I and II or almost exclusively in Lead I. There may be reciprocal shifting of the ST segments in Leads I and III in very localized areas of pericarditis which would be similar to those present in various types of myocardial infarction if similarly placed.[7] This rarely occurs clinically since pericarditis is usually diffuse. The ST elevation diminishes and disappears in a short time and the T-waves become negative.

In acute pericarditis, Q–T patterns, such as occur in early or late myocardial infarctions, are not observed. Loss of R in the apical lead and the appearance of a large Q in this lead or in Lead I, changes which are frequently associated with anterior infarction, do not occur.

Within one to six weeks, although it is sometimes longer,[8] after the acute phase of the pericarditis is over, the electrocardiogram begins to return to normal. This tendency of the electrocardiogram to return rapidly to normal is a very important point which serves to distinguish acute pericarditis

from myocardial infarction because in the latter case the change is much slower and may not be complete for years, if ever.

Acute pericarditis is not a common disease. Fifteen cases were found in a review of 11,674 electrocardiograms, an incidence of only 0.7 per cent. Many cases are probably missed because Smith and Willius [9] in a review of 8,912 autopsies at the Mayo Clinic found 373 cases, an incidence of 4.3 per cent; in 58 per cent of these 373, acute pericarditis was present. They found 12 instances of primary pericarditis (2.4 per cent). The number of cases of coronary occlusion in the same period would be much greater. In the individual patient, the importance of making the correct diagnosis is obvious because of the optimistic prognosis that can be given in acute non-specific pericarditis.

Summary

Twenty cases of acute pericarditis were studied. Fifteen of these were diagnosed from a total of 11,674 electrocardiograms taken in the 10 year period 1936 to 1946. Eight cases are presented to illustrate non-specific etiology (3), cryptic etiology (3), and unusual onset (2). The electrocardiographic changes and differential diagnosis are discussed.

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BIBLIOGRAPHY

1. Barnes, A. R., and Burchell, H. B.: Acute pericarditis simulating acute coronary occlusion, Am. Heart J. **23**: 247, 1942.
2. Wolff, L.: Acute pericarditis simulating myocardial infarction, New England J. Med. **230**: 422, 1944.
3. Burchell, H. B.: Acute non-specific pericarditis, Modern Concepts of Cardiovascular Dis. **16**: 1947, No. 3.
4. Butsch, W. L.: Acute pericarditis as a post-operative complication, Proc. Staff Meet., Mayo Clin. **12**: 737, 1937.
5. Porter, W. B.: Acute pericarditis, diagnosis and treatment of cardiovascular disease, 1945, F. A. Davis Co., Philadelphia.
6. Smalley, R. E., and Ruddock, J. C.: Acute pericarditis: a study of eighteen cases among service personnel, Ann. Int. Med. **25**: 799, 1946.
7. Burch, G., and Winsor, T.: A primer of electrocardiography, 1946, Lea and Febiger, Philadelphia.
8. Nay, R. M., and Boyer, N. H.: Acute pericarditis in young adults, Am. Heart J. **32**: 222, 1946.
9. Smith, H. L., and Willius, F. A.: Pericarditis. IV. Fibrinous pericarditis and soldier's patches, Arch. Int. Med. **50**: 410, 1932.

AUTOPSY INCIDENCE OF PULMONARY EMBOLISM IN CORONARY HEART DISEASE *

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THE incidence of pulmonary embolism in coronary heart disease has received increasing attention in the past few years, following the introduction of anti-coagulant therapy in thrombo-embolic disease. Adequate statistics are not yet available as to the efficacy of such therapy, due partly to the fact that relatively few reports on the autopsy incidence of pulmonary embolism in coronary heart disease have been published. Several such reports [1, 2, 3] dealing with the incidence of thrombo-embolic phenomena in myocardial infarction have been quoted rather frequently as providing a logical basis for Dicumarol therapy. Other reports have dealt with the causes of death in coronary thrombosis and acute coronary occlusion. Eppinger and Kennedy [4] report that 6.5 per cent of 200 consecutive deaths from coronary thrombosis died of massive pulmonary embolism, and Woods and Barnes [5] state that six of 60 deaths occurring within six weeks of an attack of acute coronary occlusion were due to massive pulmonary embolism. However, more complete statistical data, dealing not only with the incidence of pulmonary embolism in myocardial infarction but also with its incidence in those cases of coronary heart disease in which no thrombus or infarct exists, are needed. In a previous report [6] I have stressed the incidence of pulmonary embolism in nonsurgical patients with prostatic thrombosis in a study based on 635 consecutive autopsies in an institution where the average age at autopsy was unusually high (60.04 years). In this series prostatic thrombosis accounted for approximately 45.4 per cent of all pulmonary emboli in male subjects. Congestive heart failure was the outstanding etiologic factor in the development of prostatic thrombosis, being present in 36 of 84 instances. In view of the surprisingly high incidence of pulmonary embolism in this series (23.1 per cent) it seemed that a report of the incidence of pulmonary embolism in those subjects dying of coronary heart disease might be of value. As expected in this age group the number of patients dying of heart disease was high. Of the 635 subjects in the series 140 (22 per cent) died of coronary, hypertensive, rheumatic or syphilitic heart disease.

PRESENT STUDY

The present study of these 140 deaths deals primarily with the incidence of pulmonary embolism in 88 subjects who died of some form of coronary heart disease including those cases with and without thrombosis and/or

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myocardial infarction. Although the number of cases of the other three main types of heart disease is not large enough for detailed analysis, the incidence of pulmonary embolism in each group is shown in table 1.

The 88 cases of coronary heart disease have been arbitrarily divided according to a simple pathological classification. The term arteriosclerotic heart disease in this report is used to mean arteriosclerotic involvement of the coronary arteries without marked stenosis, thrombosis, or myocardial infarction. The other subdivisions are formed by adding the modifying condition. These results are shown in table 2. While the figures are of some interest in showing the relative frequency of stenosis, thrombosis, and myocardial infarction in this series, they cannot be regarded as statistically significant as far as the incidence of pulmonary embolism in each subdivision is concerned due to the small number of cases.

TABLE I

Pulmonary Embolism in 140 Deaths from Heart Disease

	Number of Cases	Massive Embolism		Minor Embolism	
		Number	Per cent	Number	Per cent
Coronary heart disease (all groups)	88	8	9.1	18	20.5
Rheumatic heart disease	13	0	0	2	15.4
Hypertensive heart disease	29	2	6.9	7	24.1
Syphilitic heart disease	10	3	30	2	20.0
Total	140	13	9.3	29	20.7

As shown in table 2 the incidence of pulmonary embolism in all forms of coronary heart disease was 29.5 per cent which is practically the same as the incidence of 30 per cent occurring in the group of heart diseases shown in table 1. The incidence of pulmonary embolism in subjects who died of heart disease is thus shown to be definitely higher than the incidence of pulmonary embolism in the entire series (23.1 per cent).

In this series emboli were diagnosed as "massive" when one half or more of the pulmonary circulation was occluded. Massive pulmonary embolism occurred 13 times in the 140 cases of heart disease included in the study to account for 9.3 per cent of these deaths. It occurred eight times in the 88 cases of coronary heart disease to account for 9.1 per cent of the deaths in this group. The contributory rôle of the minor pulmonary emboli is difficult to evaluate, but the occurrence of 11 lung infarcts in the 29 cases of minor embolism indicates that they had a bearing on the fatal outcome in at least some of the deaths.

The incidence of pulmonary embolism in cases showing myocardial infarcts and those without infarcts is practically identical. Of 20 cases with myocardial infarction six or 30 per cent showed pulmonary emboli, whereas

in 68 cases without infarction there were 20 pulmonary emboli (29.4 per cent). However, massive pulmonary embolism occurred in non-infarcted cases seven times, an incidence of 10.3 per cent, whereas it occurred in the infarcted group only once, an incidence of 5 per cent. This high proportion of massive embolism in non-infarcted cases is especially interesting as these were the cases which showed less severe damage to the heart and in which, except for the embolism, the patient would probably have recovered.

Lung infarcts occurred in 19 of the 42 subjects with pulmonary embolism (45.2 per cent) in the four groups of heart disease included. In those cases showing massive pulmonary emboli lung infarcts occurred in eight of 13, an incidence of 61.5 per cent, and in the 29 cases with minor embolism there were 11 infarcts, an incidence of 37.9 per cent. In the coronary group lung infarcts occurred with 10 of 26 pulmonary emboli (38.5 per cent), while 9 infarcts occurred with the 16 emboli found in the other three groups combined, an incidence of 56.3 per cent. This variation may be accounted for by the fact that more of the cases in the hypertensive and syphilitic heart disease groups showed congestive heart failure.

TABLE II

Subdivisions of Coronary Heart Disease

	Number of Cases	Massive Embolism		Minor Embolism	
		Number	Per Cent	Number	Per Cent
Arteriosclerotic heart disease	17	1	5.9	2	11.8
Arteriosclerotic heart disease with stenosis	43	6	13.9	10	23.2
Arteriosclerotic heart disease with thrombosis	8	0	0	1	12.5
Arteriosclerotic heart disease with myocardial infarction	2	1	50	0	0
Arteriosclerotic heart disease with stenosis and myocardial infarction	5	0	0	2	40
Arteriosclerotic heart disease with thrombosis and myocardial infarction	13	0	0	3	23.1
Total	88	8	9.1	18	20.4

In order to attempt to correlate the occurrence of pulmonary embolism with the mode of death the subjects were divided into three main groups based on the clinical picture prior to death. The first group was made up of those subjects showing definite clinical evidence of congestive heart failure at some time during the few weeks prior to death. The second group included those subjects who had been ill for some days or weeks prior to death but who had shown no clinical evidence of congestive heart failure. Many of these patients had developed intercurrent infections such as bronchopneumonia or vascular complications such as cerebral softening. The third group included those patients who had died suddenly within a few minutes to a few hours in an acute coronary attack. The presence of clinically

diagnosed congestive heart failure did not appear to affect the incidence of pulmonary embolism in the coronary heart disease group for of the 26 cases of pulmonary embolism in this group 13 developed in patients showing clinical congestive failure and 12 developed in patients with no clinical congestive failure. However, evidence of some degree of congestive heart failure was found at autopsy in most of these 12 subjects. One instance of pulmonary embolism was found in the "sudden death" group. These results are shown in table 3.

TABLE III

Mode of Death in Coronary Group

	Number of Cases	Clinical Congestive Failure	No Clinical Congestive Failure	Sudden Death
Subjects with pulmonary embolism	26	13	12	1
Subjects without pulmonary embolism	62	24	29	9

In the group showing no clinical evidence of congestive heart failure there were five subjects who died of ruptured myocardial infarcts with hemopericardium. The average age of these patients was 69 years. Symptoms of the original coronary attack which led to the myocardial infarction were mild and none of these patients had been kept at complete bed rest. No cases of rupture of the myocardium were found in subjects who had been at complete bed rest because of definite symptoms of a coronary attack.

COMMENT

The data presented confirm other reports indicating that any form of therapy that would result in the lowering of the incidence of pulmonary embolism would be valuable in the routine treatment of coronary heart disease, and although the number of cases of hypertensive, rheumatic, and syphilitic heart disease was not large enough in this series to justify statistical analysis the incidence of pulmonary embolism in these groups suggests that similar therapy may be used in these conditions to good advantage. The high incidence of pulmonary embolism due to prostatic thrombosis as reported in a previous article would suggest that anti-coagulant therapy such as Dicumarol would be more effective than venous ligation in the prevention of pulmonary embolism at least in nonsurgical patients in this age group.

SUMMARY

Pulmonary embolism occurred 42 times (30 per cent) in a group of 140 subjects who died of coronary, rheumatic, hypertensive or syphilitic heart disease in a series of 635 consecutive autopsies in an institution where the average age at autopsy was unusually high (60.04 years), and where the autopsy material was preponderantly nonsurgical. Massive embolism occurred 13 times to account for 9.3 per cent of these 140 deaths.

Pulmonary embolism occurred in 26 of 88 cases of coronary heart disease (29.5 per cent). The incidence of pulmonary embolism was the same regardless of whether or not myocardial infarction had occurred, but the incidence of massive embolism was higher in the group not showing myocardial infarction.

Lung infarcts developed in 19 of 42 cases with pulmonary embolism (45.2 per cent). In 13 instances of massive embolism infarcts were found in eight, an incidence of 61.5 per cent.

The presence of clinically diagnosed congestive heart failure did not appear to affect the incidence of pulmonary embolism in those patients who had been ill for several days or weeks prior to death. However, most of the group with pulmonary embolism which did not show clinical evidence of congestive heart failure presented some degree of congestive heart failure at autopsy.

Five cases of ruptured myocardial infarcts with hemopericardium were found in the 88 cases of coronary heart disease. All of these patients had presented relatively mild initial symptoms and none had been kept at complete bed rest.

BIBLIOGRAPHY

1. Hellerstein, H. K., and Martin, J. W.: Incidence of thrombo-embolic lesions accompanying myocardial infarction, Am. Heart J. **33**: 443–452, 1947.
2. Nay, R. M., and Barnes, A. R.: Incidence of embolic or thrombotic processes during immediate convalescence from acute infarction, Am. Heart J. **30**: 65–76, 1945.
3. Blumer, G.: The importance of embolism as a complication of cardiac infarction, Ann. Int. Med. **11**: 499–504, 1937.
4. Eppinger, E. C., and Kennedy, J. A.: The cause of death in coronary thrombosis with special reference to pulmonary embolism, Am. J. M. Sc. **195**: 104–106, 1938.
5. Woods, R. M., and Barnes, A. R.: Factors influencing immediate mortality rate following acute coronary occlusion, Proc. Staff Meet., Mayo Clin. **16**: 341–345, 1941.
6. Moran, T. J.: Pulmonary embolism in nonsurgical patients with prostatic thrombosis, Am. J. Clin. Path. **17**: 205–208, 1947.

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BIBLIOGRAPHY

1. Hellerstein, H. K., and Martin, J. W.: Incidence of thrombo-embolic lesions accompanying myocardial infarction, Am. Heart J. **33**: 443–452, 1947.
2. Nay, R. M., and Barnes, A. R.: Incidence of embolic or thrombotic processes during immediate convalescence from acute infarction, Am. Heart J. **30**: 65–76, 1945.
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4. Eppinger, E. C., and Kennedy, J. A.: The cause of death in coronary thrombosis with special reference to pulmonary embolism, Am. J. M. Sc. **195**: 104–106, 1938.
5. Woods, R. M., and Barnes, A. R.: Factors influencing immediate mortality rate following acute coronary occlusion, Proc. Staff Meet., Mayo Clin. **16**: 341–345, 1941.
6. Moran, T. J.: Pulmonary embolism in nonsurgical patients with prostatic thrombosis, Am. J. Clin. Path. **17**: 205–208, 1947.

RESPIRATORY MANIFESTATIONS OF DORSAL SPINE RADICULITIS SIMULATING CARDIAC ASTHMA *

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In a previous study attention was called to the syndrome of dorsal spine radiculitis with attacks of substernal and precordial pain simulating coronary occlusion.[1] It was shown that such attacks were frequently accompanied by a peculiar respiratory distress described most often as an inability to take a deep breath. This discomfort was noted not only during severe paroxysms of pain, but at times after chest pain had abated or ceased. In several instances, it could be induced together with chest pain by the application of pressure over the dorsal vertebrae, and a few patients found it more distressing than the induced pain.

The purpose of the present communication is to show that respiratory distress may be the only or major manifestation of dorsal spine radiculitis, and sometimes simulate attacks of cardiac asthma. The three patients reported here were thought to have cardiac dyspnea before the spinal origin of the symptom was established.

Case 1. A 62 year old housewife had been under observation since 1938 following a radical mastectomy for carcinoma. When seen on March 30, 1946, she complained of nocturnal attacks of paroxysmal respiratory discomfort and "shortness of breath," of two months' duration. These attacks woke her out of her sleep, and were accompanied by weakness, flushing, sweating, and at times a very mild "achy" sensation in the upper anterior and posterior chest regions. The need for "more air" would take her to an open window or porch. She was conscious of an inability to breathe deeply. The respiratory rate was usually normal. At times it was slow, occasionally rapid and shallow. The attacks varied from a few minutes to a half hour in duration and were not accompanied by wheezing or cough. At first, attacks occurred once or twice a week; later they became more frequent and severe. She thought she had developed slight dyspnea on exertion and occasionally had mild attacks of respiratory distress during the day. Physical examination was negative except for a few medium-sized, consonating râles at the lower right axilla. A chest plate was negative. The electrocardiogram was entirely within normal limits. An exercise tolerance test showed a normal response of pulse and respiration.

The possibility of cardiac asthma was considered although the history was not typical, and absolute bed rest recommended. The possibility of anxiety as the cause was considered but excluded. She was known by the examiner for 10 years as a happy, well-adjusted, industrious woman. She had reacted well to her breast condition. There was no past history of psychosomatic complaints, phobias, or panics, and no recent emotional disturbances.

In the course of three weeks of bed rest, the attacks became progressively more frequent, more severe, and of longer duration, and now occurred as often during the day as at night. An able physician who observed her in the course of an attack, thought that she was most likely suffering from cardiac asthma. The patient, how-

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ever, somewhat facetiously suggested that the bed rest might be the cause of the increased frequency and severity of the attacks.

April 21, 1946, she was admitted to the Beth Israel Hospital for study. A decholin velocity time was 14 seconds. Her suggestion that bed rest might have aggravated her condition made me suspect the spine for the first time. Examination at this time showed exquisite tenderness over the first to the seventh dorsal vertebrae and marked tenderness over the second and fourth left and third and fourth right costochondral junctions of the corresponding ribs anteriorly. Firm pressure over the third and fourth vertebrae slightly to the left of the spinous processes produced immediate pain starting at the point of pressure and radiating around the left breast to the sternum. Simultaneously she complained of an inability to breathe. She stated that her chest felt "fixed," that she was unable to move it to take air in or out. She complained of weakness and perspired, and volunteered that this was similar to the nocturnal attacks she had complained of. After a few minutes, a second attack was reproduced by the same procedure.

She was seen the next day by an orthopedist, Dr. Samuel S. Hanflig. He noted a moderately increased dorsal curve, tenderness in the region of the thoracic spine, particularly over the eighth, ninth, and tenth vertebrae with pressure in this area causing pain around the lateral chest wall.

During the next few days, she was very uncomfortable with more or less continuous pain over the upper dorsal spine and with repeated attacks of respiratory distress, more severe than at home. She said that "pounding" on her spine had definitely aggravated her condition and had brought out pain not experienced before. On two or three occasions the intern was called at night to prescribe medication. His note is as follows: "She complained of severe bilateral and unilateral lower thoracic discomfort, a kind of constricting pain involving the lower third of her thorax anterolaterally. There was nausea, belching, and the complaint of severe dyspnea, but no change in respiration, heart rate, rhythm, blood pressure, and the only objective sign was the obvious suffering of the patient and a facial pallor which followed the attack. At times the constricting sensation was in the upper abdomen rather than the lower thorax."

On the ninth hospital day, she was put on cervical traction. There was a definite decrease in the number of attacks after the first 24 hours. After two days of almost constant traction, however, it was discontinued because of development of pain in the temporo-mandibular joints, general muscular aches and pains, and continuous vomiting. During the next two days, there was a sharp increase in the number and severity of her chest episodes. After vomiting stopped, traction was resumed and all symptoms progressively improved.

Roentgen examination showed advanced osteoarthritic changes with spur formations about the margins of the bodies of the lower cervical and upper dorsal vertebrae. Changes were most marked in the lower cervical region, where there were spurs along the posterior margins, marked narrowing of the intervertebral spaces, and slight narrowing of the intervertebral foramina.

She remained free of symptoms during the next 10 months after which she began to have severe anterior chest and shoulder-girdle pain, worse in bed, and aggravated by prolonged sitting. These symptoms responded only partially to orthopedic measures, and she still has some periodic bouts of chest discomfort. Respiratory distress, however, has not recurred during the past two years.

Case 2. A 62 year old male was first seen December 11, 1946, complaining of recurring nocturnal attacks of respiratory distress of six months' duration. His most severe attack occurred the night before. It woke him out of sleep and persisted for approximately 90 minutes. The respiratory difficulty was described as an inability to breathe deep enough or at times to breathe at all. Associated with it there was mild upper sternal distress, a choking sensation in the neck, and epigastric discomfort

with belching. The anguish caused by the respiratory distress, however, overshadowed these symptoms. Prior to this severe attack, he had many of shorter duration, all occurring in the early morning hours between 4 and 5 a.m. On a few occasions, similar mild spells of a few minutes' duration occurred in the day time. There was no dyspnea or chest pain on exertion. Occasionally he had "vertigo spells," particularly on suddenly changing the position of his head. These were characterized by a sense of imbalance and a feeling of falling. Room objects did not move. The major episode the night before was preceded by considerable stiffness of his neck.

For the past year, he complained of vague abdominal discomfort associated with mild respiratory distress of the same kind. It was not related to eating or associated with nausea or vomiting.

Physical examination showed slow regular heart sounds of good quality and no murmurs. Blood pressure was 130/60 mm. Hg. The lungs were clear. There was moderate local tenderness over the second to sixth dorsal vertebrae, but no referred pain. Rotation of the neck to the right was limited. An electrocardiogram was entirely within normal limits. While we were discussing the problem another attack occurred. Respiration was slow and apparently labored. He complained that it was difficult to take air in or out, of a choking sensation in his neck, and discomfort in the region of the umbilicus.

The effect of manual traction on the attack was then tested. He was placed diagonally across the bed in the supine position and, with his head resting on the examiner's left hand, traction was applied to the chin and occiput. With a pull of approximately 25 to 50 pounds, toward the examiner, there was prompt relief of all distress. A few seconds after traction was released there was an immediate return of symptoms. Manual traction was again applied and continued with less force for five minutes. During this period, the respiratory distress, the choking sensation, and the abdominal discomfort decreased and finally disappeared. The response to orthopedic treatment, traction and exercise, was good, and during the next few months attacks did not recur in spite of activity.

Case 3. A 68 year old hardware store proprietor was first examined December 29, 1940, for two recent attacks of severe substernal, vise-like, constricting pain, coming on in the course of hard physical work, and lasting approximately 30 minutes. Both attacks were followed by marked weakness of several hours' duration. He also complained of slight dyspnea on exertion, somewhat progressive during the past two years, and of a non-productive cough. He gave a history of "arthritis" with joint pains and periodic attacks of shoulder-girdle pain, worse in damp weather for the past few years. Physical examination was negative, except for sibilant rhonchi, medium-sized consonating râles at the right base and slight expiratory difficulty. Blood pressure was 140/80 mm. Hg. An electrocardiogram showed a flat or very slightly inverted T-wave in Lead II, inverted T_3, a normal CR_4, and marked left axis deviation.

During the next four and a half years, he was seen approximately 20 times for recurring bouts of severe substernal pain, often relieved only after morphine and lasting from a few minutes to several hours. Most of these attacks occurred at night; several in the course of his daily activity, particularly after excessive physical work. A few short attacks occurred in the course of walking and appeared to be relieved by rest and nitroglycerin, although the relationship was not clear. The usual sequence during this period was as follows: weeks to months of moderately strenuous activity free from chest pain; a severe attack; bed rest; and an increase in symptoms with recurring attacks while in bed. Each time the question of infarction was raised, but not a single episode was followed by a rise in temperature, leukocytosis, or progressive electrocardiographic changes. On several occasions he refused to remain

in bed and after getting up and about felt better. For this reason, the possibility of pain of spinal origin, in addition to coronary disease was raised. Repeated examinations showed some tenderness on either side of the sternum and the upper dorsal spine with no referred pain. Roentgen-rays of the spine showed advanced hypertrophic changes with large spur formations about the margins of the bodies of the cervical and dorsal vertebrae. Changes were most marked in the middle and lower dorsal regions with marked bony bridging in these areas. There was narrowing of the intervertebral spaces in the lower cervical and dorsal regions. The bones of the spine showed a marked degree of osteoporosis.

On July 9, 1945, four and a half years after the onset of these attacks, he first complained of bouts of respiratory distress, consisting of difficult and at times rapid breathing, of one to five minutes' duration. A few attacks occurred during the day, but most occurred during the night, often waking him from sleep. He developed one attack during an examination. The respiratory rate rose from 20 to 32. Physical examination showed a grossly irregular ventricular rate of 85, and a few scattered consonating râles and rhonchi at both bases, findings noted in the past and considered a part of his bronchial asthma and chronic bronchitis. The electrocardiogram showed auricular fibrillation, but was otherwise unchanged. Bed rest was prescribed and a few days later the rhythm was regular. Respiratory distress did not recur, but chest pain appeared and became increasingly severe and continuous. As soon as he was permitted up out of bed, the pain became less marked and subsided entirely within a few days.

Six months later he again developed nocturnal attacks of precordial and epigastric pain, this time associated with respiratory distress. One very severe attack of substernal pain and weakness was accompanied by a nausea which persisted all night. With absolute bed rest this time, the pain became less frequent, but bouts of respiratory distress became more frequent. Examination of his lungs again showed only sibilant rhonchi and occasional medium sized consonating râles at the right base. The effect of activity was tested and the respiratory distress promptly subsided.

He remained active, in good physical condition, for the next five months, and up to the time he moved to his summer cottage. The first night in a bed that sagged greatly he began to have attacks of respiratory distress, described as an inability to breathe. The respiratory rate was not increased. Attacks often woke him up from sleep and generally persisted for one to three hours. Absolute bed rest was insisted upon because the examiner was still not certain that the attacks were not of cardiac origin. As a result, the respiratory condition grew worse. Attacks now occurred with equal frequency during the day and were definitely related to his position in bed. As long as he sat straight up in bed for hours they did not occur, whereas, after reclining, they reappeared within a few minutes. Improvement was dramatic following the use of bed boards at night and full activity during the day. During the past year, there has been no recurrence of respiratory distress. On occasion, he has had some substernal pain related to changes in bodily position. There has been no evidence of circulatory failure.

Discussion

This type of respiratory distress was most often described by the patient as an inability to inspire or expire and an awareness that breathing was disturbed, difficult and consciously forced. Common statements were: "My breathing is cut off—I can't breathe in or out—I can't take a deep breath—My chest seems fixed—I find I must force myself to breathe." Most patients observed during attacks showed no increase in the respiratory rate, but a few had unmistakable bouts of hyperpnea. The respiratory move-

ments in one patient during the induction of chest pain were suspended for a few seconds, and then followed by a short bout of hyperpnea. She complained that her breathing was "cut off," and that she could not take a deep breath. Another patient (Case 3) showed hyperpnea during an attack that occurred during an examination, but on other occasions and during periods of prolonged respiratory distress, the respiratory rate was not increased. It is quite possible that the hyperpnea in some instances was an emotional reaction to the dilemma of being unable to breathe normally.

It is generally appreciated that respiratory symptoms ranging from sighing respirations to hyperpnea are common psychosomatic complaints. In this category particularly frequent is the complaint of air hunger, of being unable to get enough air in even after a deep breath. In contrast to this particular variety, the respiratory distress in the radicular syndrome is more often an awareness that inspiration or expiration is inhibited. Most patients find it especially difficult to describe this symptom, and even with an accurate description the possibility of psychogenic origin must be considered and eliminated. A patient first seen with this complaint in 1940 very definitely raised the question of a psychogenic origin. Unlike the three patients presented here, his symptoms were only of seconds' duration and did not suggest cardiac dyspnea. Lengthy and detailed study showed no evidence of emotional cause. The first clue as to the real nature of the respiratory symptoms occurred only months later when he began to have chest pain with unmistakable radicular characteristics.

The patients reported here were selected because they were singularly free of nervous symptoms and capable of giving a reliable history. At one time or another, they had respiratory symptoms without chest pain and Case 1 illustrates the presence of disturbing symptoms of this kind as a major complaint long before chest pain appeared. Respiratory symptoms without simultaneous chest pain, however, are not very common. Only six examples were encountered during the past two years, and even these patients either had chest pain before or developed it later. On the other hand, approximately 35 per cent of those with radicular chest pain show simultaneous respiratory distress at some time. In a group of 43 patients recently studied for the roentgen findings of the cervical and dorsal spine, 16 had such symptoms.[2]

Patients with angina pectoris sometimes complain of a similar breathing difficulty during the attack itself and, therefore, respiratory distress of spinal origin might easily be mistaken for a manifestation of coronary disease, particularly when also associated with chest pain however atypical. Transient bouts of hyperpnea, of course, would raise the question of cardiac asthma. The author considered this possibility in Cases 1 and 3, although the attacks were atypical and hyperpnea generally absent.

The mechanism of this symptom is not known. Motor involvement, however, with muscle spasm is very common in nerve root irritation of the cervical spine, and patients with dorsal spine involvement likewise frequently

show spasm of muscles of the chest wall. It is probable, therefore, that the respiratory symptoms are in some way related to spasm of the accessory muscles of respiration.

The recognition of the spinal origin of this symptom will not be difficult if its possibility is entertained in differential diagnosis. The response to effort, routine examination of heart and lungs, the electrocardiogram and chest plate, the velocity of circulation, and the response to rest and digitalization will help to rule out congestive heart failure, bronchial asthma, emphysema, and less common types of mediastinal and pulmonary disease. A careful search for psychosomatic symptoms, inquiry as to panic reaction, phobias, and a study of the patient's life situations with an evaluation of his aggressions and defenses will help to determine whether or not nervous factors are responsible. The final diagnosis, however, has to be based on positive evidence of nerve root irritation. A history of chest pain with radicular characteristics, the relation of respiratory distress to a given bodily position such as reclining or sitting, costochondral and dorsal spine tenderness, the reproduction of symptoms by pressure over the dorsal vertebrae, roentgen evidence of hypertrophic arthritis of the spine and particularly the therapeutic response to traction and other orthopedic measures will lead to a correct diagnosis in most instances.

BIBLIOGRAPHY

1. Davis, D.: Spinal nerve root pain (radiculitis) simulating coronary occlusion: a common syndrome, Am. Heart J. **35**: 70–80, 1948.
2. Davis, D., and Ritvo, M.: The clinical and roentgen findings in osteoarthritis of the cervicodorsal spine (radiculitis) simulating coronary artery disease, New England J. Med. **238**: 857–866, 1948.

CASE REPORTS

STREPTOMYCIN IN THE TREATMENT OF *PROTEUS VULGARIS* MENINGITIS *

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Proteus vulgaris meningitis is relatively uncommon. It may occur by direct extension from an adjacent otitis media or mastoiditis and occasionally as a complication of septicemia from a focus of infection, usually in the genito-urinary tract. The causative organism is a gram-negative, aerobic, non-sporulating, actively motile bacterium, usually occurring as a saprophytic non-pathogen in the upper respiratory, gastrointestinal, or genito-urinary tracts. Occasionally it produces severe infection and death.

In a review of the literature Abrams [1] states that approximately four-fifths of patients under 40 years of age with *Proteus vulgaris* septicemia had middle ear infection and of those over 40 years of age, about four-fifths had primary genito-urinary tract disease. In 48 cases, 64.6 per cent died, and 35.4 per cent recovered. In the genito-urinary tract group of cases the mortality was 36.8 per cent, whereas in the ear, nose and throat group of cases the mortality was 80.1 per cent.

Prior to the use of streptomycin to treat *B. proteus* meningitis the mortality rate exceeded 90 per cent. Therapy consisted of mastoidectomy, the use of bacteriophage and vaccines. In a few instances in the literature, the mortality rate was reduced by sulfonamides. In the National Research Council report [2] on streptomycin, three cases of *B. proteus* meningitis, one due to *B. proteus morgani* and two due to *B. proteus vulgaris*, were treated with streptomycin. One of the patients with *B. proteus vulgaris* meningitis died and the other two survived. Paine et al.[3] reported curing a four month old infant who developed *B. proteus morgani* meningitis following operation on a congenital meningocele. The favorable result was caused by streptomycin given intramuscularly and intrathecally, although sulfadiazine was used concurrently during the last four days of the streptomycin therapy. Abrams [1] reported the striking effect of streptomycin in a 44 year old man with *Proteus vulgaris* septicemia secondary to renal calculi. Kaplan and Poweleit [4] reported curing a patient with *Proteus vulgaris* meningitis following chronic otitis media and complicated by thrombosis of the left internal jugular vein. Treatment consisted of ligation of the jugular vein, and the administration of streptomycin, penicillin and sulfadiazine. The authors were not impressed with the value of streptomycin.

B. proteus has a high resistance to penicillin, 5 to 10 units per ml. being necessary to inhibit the organism.[5, 6, 7, 8] On the basis of this relatively high resist-

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ance, the use of penicillin in *B. proteus* meningitis is not indicated. *B. proteus* is moderately sensitive to streptomycin in vitro, being inhibited by 2 to 8 units per ml.[9, 10, 11] Chick embryos are protected by it against experimental infection with *B. proteus*.[12] To aureomycin *B. proteus* has proved most resistant in vitro and in vivo.[13] The organism, however, has been demonstrated to be sensitive in vitro to less than 1 microgram per ml. of chloromycetin.[14, 15] On this basis, chloromycetin should prove effective in clinical infections caused by *Proteus vulgaris*, and should be tried clinically in cases of *Proteus vulgaris* meningitis. It seems apparent that streptomycin and perhaps chloromycetin are the drugs of choice in treating *Proteus vulgaris* infections. The cases presented in this report were treated prior to the availability of chloromycetin. The following is a report of two cases of *Proteus vulgaris* meningitis successfully treated with streptomycin.

Case Reports

Case 1. A 59 year old Caucasian male was admitted to the Communicable Disease Unit of the Los Angeles County General Hospital on January 25, 1948, complaining of a stiff neck and headache of four days, and chills and fever for two days prior to admission. Several teeth were extracted on January 19 and 22 because of severe pyorrhea. There was a history of a chronic draining left ear. Except for steady weight loss for one year the patient thought he had been in good health. There was no history of any severe illness. A hemorrhoidectomy was performed in December 1947.

Physical examination revealed an acutely ill patient showing marked weight loss, with evidence of slow cerebration, and appearing older than his stated age of 59 years. The temperature was 104° F., the pulse 104, the respirations 22, and the blood pressure 138 mm. Hg systolic and 55 diastolic. The pupils were equal, reacted to light and accommodation, and the extra-ocular movements were grossly normal. He was unable completely to close the left eye. The right ear was negative. The left external auditory canal was filled with sero-sanguinous fluid and a granulomatous lesion was seen on the anterior wall. The drum was not visualized. There was flattening of the left side of the face and drooping of the left side of the mouth. The oral cavity was foul with evidence of recent dental surgery; the wounds discharged purulent material. The neck was extremely rigid. The heart, lungs and abdomen were normal. Neurological examination disclosed normal physiological reflexes and negative Kernig and Brudzinski signs.

The urinalyses were negative. A blood count on admission revealed hemoglobin 15 grams and white cell count 18,150 with 84 per cent neutrophiles. The CO_2 combining power was 49 volumes per cent. The non-protein nitrogen was 34 mg. per 100 c.c. blood. The spinal fluid was cloudy, pressure 225 mm. of water, Pandy one plus, sugar normal, and 5,000 white cells with 92 per cent neutrophiles.

Treatment was started with large doses of sulfadiazine and sulfamerazine in equal parts, together with penicillin intravenously and intramuscularly. *Proteus vulgaris* was reported the following day from the spinal fluid cultured at the time of admission to the hospital. The blood culture was reported negative. When the etiological agent was determined the patient was started on large doses of streptomycin and the sulfonamides were discontinued. Four grams were given the first 24 hours in divided doses every four hours, followed by three grams each 24 hours for 48 hours, two grams each 24 hours for three days and finally one gram in divided dosage for 24 days. One-tenth gram was given intrathecally daily for the first 13 days. On the second hospital day the spinal fluid contained 220 cells and on the thirty-second day 2 cells.

The first week of hospitalization was stormy. The temperature ranged from 101° to 104° F. for seven days, then gradually fell to normal. Biopsy of the lesion in the

left auditory canal proved to be a squamous cell carcinoma, grade 1 or 2. Subsequent cultures of the spinal fluid and discharge from the left ear were negative for *Proteus vulgaris*. Twenty-eight days after hospitalization the patient was transferred to another department for treatment of the carcinoma. Operation was performed on March 11, but the lesion was found to invade the bone and was not curable by surgery. The patient, however, survived the exploratory surgery and was discharged subsequently from the hospital.

Case 2. An 18 year old Chinese male was admitted to the Communicable Disease Unit of the Los Angeles County General Hospital on November 28, 1947, complaining of right ear ache associated with chills and fever for one week prior to admission, and severe headache and stiffness of the neck for 24 hours. There was a history of a chronic right draining ear for a period of 10 to 15 years. The past history, except for the chronic otitis media and malaria at the age of eight years, was essentially negative.

On physical examination the patient was noted to be moderately toxic and somewhat lethargic, but when aroused was able to answer direct questions and was well oriented. The temperature was 100° F., the pulse 110, the respirations 24, and the blood pressure 120 mm. Hg systolic and 70 diastolic. There were a few scattered petechiae over the abdomen and upper right arm. Acne of the face, back and chest was present. The pupils were equal and reacted well to light. The extra-ocular movements were grossly normal. Except for an old, well healed perforation, the left ear appeared normal. The right external canal was filled with a thick, purulent exudate which had a foul odor. After removal of the exudate from the canal a well defined central perforation was noted with exudate coming through. There was no external evidence of mastoiditis. The nose and throat were normal. The neck was rigid. The cervical nodes were enlarged and moderately tender. Examination of the chest, heart and abdomen was normal. There were positive Kernig and Brudzinski signs. The reflexes were within normal limits.

Urinalysis was negative. The white cell count was 19,700 with 98 per cent neutrophiles. The CO_2 combining power was 50 volumes per cent. The non-protein nitrogen was 32 mg. per 100 c.c. blood. The spinal fluid pressure appeared normal, with normal rise and fall. The fluid was cloudy, sugar reduced, Pandy four plus, and white cell count 9,000 with 100 per cent neutrophiles.

A diagnosis of purulent meningitis, probably secondary to chronic otitis media and mastoiditis was made. Roentgen-rays of sinuses and mastoids confirmed the presence of bilateral mastoiditis with bony destruction of the right mastoid. Intensive chemotherapy and antibiotic therapy was started. He received a blood transfusion in addition to intravenous fluids. A radical right mastoidectomy was performed the night of admission. A large cholesteatoma found in the attic was removed. An epidural abscess was noted and adequately drained. The post-operative condition of the patient was fair. A pure culture of *Proteus vulgaris* was obtained from the pus found in the middle ear. The initial blood culture was positive for *Proteus vulgaris*. Spinal fluid culture taken at the time of admission also grew out *Proteus vulgaris*. Smears and cultures of the petechiae were reported negative. The following morning the spinal fluid contained 345 cells with 75 per cent neutrophiles. The culture was negative.

With identification of the causative organism, the patient was placed on streptomycin 0.5 gram intramuscularly every four hours for a period of three days and then every six hours for three days. On the sixth day of streptomycin therapy, the patient showed signs of toxicity and dosage was reduced to 0.25 gram every six hours. The extreme vertigo and tinnitus of the left ear, however, continued and streptomycin was discontinued. Sulfadiazine and sulfamerazine with adequate sodium citrate to keep the urine strongly alkaline were continued. The spinal fluid returned to normal

in eight days. Subsequent blood cultures were without growth. The last positive culture for *Proteus vulgaris* from the operative site was on November 29, 24 hours after admission. The patient had a rather uneventful convalescence and all medication was discontinued on the eighteenth hospital day. Three days later the patient was transferred to another service where he remained until he was discharged on December 28, after 30 days of hospitalization. Except for a slight amount of granulation tissue around the surgical wound which was treated in the out-patient clinic, the patient remained well.

Discussion

Two cases of *Proteus vulgaris* meningitis, one with septicemia, both secondary to mastoiditis, and both cured with streptomycin, are reported. Both patients received as part of their original treatment sulfadiazine and sulfamerazine. The first case received sulfonamides for less than 24 hours. This patient's mastoiditis was complicated by a squamous cell carcinoma of the left auditory canal. The second case was complicated by a large cholesteatoma and epidural abscess which required a radical right mastoidectomy and drainage of the epidural abscess in addition to antibiotic therapy. Prior to streptomycin therapy *Proteus vulgaris* meningitis always had an extremely high mortality rate. The use of streptomycin in these two cases was largely responsible for their favorable outcome. Probably a high initial dosage of streptomycin is indicated: e.g., three to four grams in divided dosage for 24 to 48 hours, gradually decreased thereafter, to prevent irreversible damage to the auditory mechanism. If signs and symptoms of streptomycin toxicity develop and persist after reduction in the amount of streptomycin, as occurred in Case 2, sulfonamide therapy should be started. However, now that chloromycetin is available, the combined use of streptomycin and chloromycetin may be the treatment of choice. We prefer the intrathecal and intramuscular administration of streptomycin in the treatment of meningitis. One-tenth gram of streptomycin intrathecally daily is given. If untoward signs or symptoms of meningeal irritation develop, the intrathecal dosage is reduced to one-twentieth gram of streptomycin.

Summary

Two cases of *Proteus vulgaris* meningitis successfully treated with streptomycin by intrathecal and intramuscular routes are reported. Streptomycin and possibly chloromycetin are believed to be the drugs of choice in the treatment of this condition. The two cases reported were treated prior to the availability of chloromycetin. In the future, the combination of streptomycin and chloromycetin will be used instead of streptomycin and sulfonamides. Early surgical intervention of known foci of infection is indicated in the management of this type of case.

BIBLIOGRAPHY

1. Abrams, H. L.: Septicemia due to *Proteus vulgaris*. Review of the literature and report of a case cured by streptomycin, New England J. Med. **238**: 185–187, 1948.
2. Committee on Chemotherapeutics and Other Agents. National Research Council, J. A. M. A. **132**: 70, 1946.
3. Paine, T. F., et al.: Streptomycin in the treatment of certain gram-negative bacillus infections of the central nervous system, Am. J. M. Sc. **213**: 676–685, 1947.

4. Kaplan, M. Z., and Poweleit, A. C.: *Proteus vulgaris* meningitis, Am. J. Dis. Child. **77**: 454–459, 1949.
5. Abraham, E. P., et al.: Further observations on penicillin, Lancet **2**: 177–188, 1941.
6. Fleming, A.: On the antibacterial action of cultures of a penicillium, etc., Brit. J. Exper. Path. **10**: 226–236, 1929.
7. Helmholz, H. F., and Surg, C.: Bacterial action of penicillin commonly present in infections of the urinary tract, Am. J. Dis. Child. **68**: 236–242, 1944.
8. Jeffrey, J. S., and Thomson, S.: Penicillin in battle casualties, British M. J. **2**: 1–4, 1944.
9. Buggs, C. W., et al.: The in vitro action of streptomycin on bacteria, J. A. M. A. **130**: 64–67, 1946.
10. Knop, C. Q.: Experimental study of the development of resistance to streptomycin by some bacteria commonly found in urinary infections, Proc. Staff Meet., Mayo Clin. **21**: 273–276, 1946.
11. Reiman, H. A., et al.: Streptomycin for certain systemic infections and its effect on the urinary and fecal flora, Arch. Int. Med. **76**: 269–277, 1945.
12. Ordal, Z. J., and Meyer, E.: The effect of streptomycin on proteus infections of the chick embryo, Jr. Bact. **52**: 67–70, 1946.
13. Collins, H. S., et al.: Aureomycin—a new antibiotic, Ann. Int. Med. **29**: 1077–1092, 1948.
14. Gottlieb, D., et al.: Some properties of antibiotic obtained from species of streptomyces, Jr. Bact. **55**: 409–417, 1948.
15. Smith, R. M., et al.: Chloromycetin: biological studies, Jr. Bact. **55**: 425–448, 1948.

SPONTANEOUS BULLA FORMATION IN THE SKIN IN DIABETES MELLITUS*

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The sudden appearance of bullae in the skin without apparent cause is not uncommon in patients with diabetes mellitus. The prevailing opinion concerning the etiology appears to be that the bulla results from an occlusion of the arteriole supplying that particular area of the skin with resulting localized necrosis. Such an explanation is plausible in view of the pathologic changes known to occur in the arterial vessels in diabetes. That another factor or factors may be involved was suggested by the following two cases observed during the past year.

Case Reports

Case 1. A white male, age 63, was admitted to the Jefferson Davis Hospital on June 18, 1948 because of hiccough, vomiting, and blisters on the feet. He had been in the hospital on several occasions during the past 10 years. His diagnosis on discharge two months previously had been arteriosclerotic heart disease and diabetes mellitus. The diabetes had not been very well regulated for its known duration of 10 years. He had taken 20 units of protamine zinc insulin daily more or less erratically and his blood sugar level had never been found to be high. Episodes of dyspnea with slight edema of the legs had occurred several times during the past few years.

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Several days before the present admission, he developed a blister on the sole of the right foot, followed the next day by another on the left foot. He had been confined to bed by the gastrointestinal disturbance mentioned above for about a week previous to the appearance of the bullae. There was some soreness about the lesions and diffuse pains were present throughout both lower extremities. The bullae were essentially symmetrical (figure 1) and contained a serous fluid which later became seropurulent; there was only a very narrow rim of erythema about them. Boric acid compresses were applied locally and penicillin was administered parenterally. The bullae broke and shallow ulcers formed which became covered by crusts. After one month the lesion on the right was healed but the one on the left still showed a small unhealed area after three months.

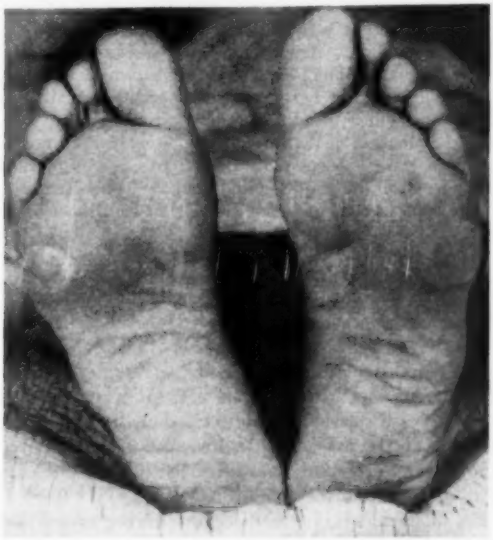

FIG. 1. *Case 1.* Bilateral symmetrical bullae. Shallow ulcers remained after separation of the overlying skin.

The pulsations in both popliteal and dorsalis pedis arteries were good but none could be felt in either posterior tibial. The tilt test showed an abnormal blanching and a diminished rate of filling in the vessels of both legs. There was an absence of vibratory sense below both knees and a diminished sense at the knees. The knee jerks were sluggish but equal. The spinal fluid drawn two weeks after the bullae had formed, was negative.

Later questioning revealed that the patient had had several episodes of bulla formation on the feet during the preceding seven years. He did not remember the exact locations but stated that they were usually bilateral, coming on without obvious cause and lasting six to eight weeks.

Case 2. A white female, age 63, had been followed off and on for the past 10 years. She had a mild diabetes readily controlled by diet and 10 units of protamine zinc insulin daily. When first seen retinal hemorrhages had recently occurred and her vision was considerably impaired. Peripheral vascular disease was apparent in

both lower extremities with an ulcerated callus on the medial aspect of the right metatarsophalangeal joint. The pulsations were not palpable in either dorsalis pedis arteries; those of the posterior tibial arteries were present, but disappeared within the next five years. Atrophy of the tissues at the base of the left big toe progressed over the past several years. In 1945 she had two episodes of myocardial infarction followed by left heart failure on several occasions. She improved gradually but her activity remained considerably curtailed because of her cardiac state and intermittent claudication.

On February 14, 1948 while resting (mostly in bed) following a respiratory infection the patient developed severe pain in the back, hips, and legs requiring opiates for relief. During the episode the skin of the lower extremities became colder than usual but the pulsations in both femorals, which were fairly good, remained unchanged. Two days later when the pain had almost subsided a bulla appeared on the medial aspect of the right big toe. It was ovoid in shape, measured 3 by 1.5 cm. and contained a serosanguinous fluid. After about two weeks when the covering of the blister was removed, a shallow but completely denuded ulcer, equal in size to the bulla, remained. Tyrothricin cream (Tyroderm) was applied locally. The ulcer healed slowly and after seven months there still remains a small uncovered area.

Neurological examination of the lower extremities showed normal ankle and knee jerks. Vibratory sense was absent in the left foot; it was markedly diminished in the right foot but normal in the right leg and above. Touch sensation was diminished in the region of the bulla of the right foot and absent over most of the left foot.

Comment

References in the available literature to spontaneous bullae in diabetes are not very numerous. Bullae accompanying extensive gangrene from the occlusion of larger arteries or bullae from trauma or infection should not of course be confused with the condition under discussion. Kramer [1, 2] refers to a number of cases of spontaneous blebs in diabetics and gives an excellent description of the onset and course of the lesions. He feels that their presence suggests active pathological changes in the arteries. In his cases usually more than one blister was seen and both feet were sometimes affected; in only one of his patients were the blebs seen to appear in successive crops.

In Case 1 the bilateral symmetrical lesions having onsets within 24 hours of each other and the history of similar episodes in the past do not favor arterial occlusion as the sole etiological factor. In Case 2 the appearance of the bulla following closely a neurological crisis not incompatible with diabetic tabes suggests a relationship between the two. Both patients have distinct circulatory insufficiency of the feet and both have definite neurological changes in the lower extremities.

Jordan et al.[3] feel that approximately 50 per cent of diabetic patients show evidence of a disturbed nervous system. Lesions have been described in the brain, spinal cord, posterior nerve roots, and peripheral nerves. That pathologic changes in the nervous system may cause or predispose to various skin lesions is also generally accepted; well known examples are herpes zoster and trophic ulcers and vesicles. Therefore it would seem logical to conclude that the nervous involvement in diabetes often plays a rôle in the skin lesions of that disease. Of course the nervous lesions themselves may be secondary to arterial changes.

Undoubtedly the atherosclerotic process in the local arteries is a necessary and probably the most important factor in this bulla formation. Also it is

always difficult to rule out trauma and low grade infections, particularly of the fungus type, in these apparently spontaneous lesions. However, in the two patients presented and in others reviewed in the literature it would appear that other processes must also be concerned. It is suggested that the nervous disturbance is one of these unknown factors.

SUMMARY

1. Two cases of spontaneous bulla formation on the feet of diabetics are presented.

2. The suggestion is made that one or more other etiological factors, besides that of arterial damage, are responsible. It is further suggested that neurological disturbances may be such a factor.

BIBLIOGRAPHY

1. Kramer, D. W.: Early or warning signs of impending gangrene in diabetes, M. J. and Rec. **132**: 338, 1930.
2. Kramer, D. W.: Peripheral vascular diseases, 1948, F. A. Davis Company, Philadelphia.
3. Jordan, W. R., Randall, L. O., and Bloor, W. R.: Neuropathy in diabetes mellitus, Arch. Int. Med. **55**: 26, 1935.

TRANSIENT ALLERGIC GASTRIC EDEMA: REPORT OF GASTROSCOPIC OBSERVATIONS DURING ASTHMATIC ATTACKS*

By JACOB LICHSTEIN, M.D., and MAX BENJAMIN, M.D., *Los Angeles, California*

THE subject of gastrointestinal allergy remains a controversial one filled with much surmise. Especially does this apply to gastric disorders where the correlation between clinical manifestations and pathologic change is meager, and where obtaining such evidence is difficult with our present means of investigation. In particular, elucidation is needed in the relationship between gastrointestinal allergy to atopy elsewhere, i.e., bronchial asthma, urticaria and allergic rhinitis.

For these reasons, objective findings and observations of the gastric mucosa in the allergic state are valuable. It is, therefore, deemed worthy of note to report the changes in the interior of the stomach as observed by gastroscopy in a case of bronchial asthma and urticaria in which the gastroscopic maneuver acted as a trigger mechanism for setting up rather profound changes.

CASE REPORT

A 48 year old white male was first seen February 1947 in the hospital with persistent headache and epigastric pain. The headache was of a recurrent pulsating character lasting from two to three weeks, and at times was localized over the right eye. It did not respond to analgesics.

He had been a known asthmatic for many years, and was subject to skin rashes.

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From the Gastrointestinal Clinic of the Los Angeles County Hospital, and Graduate Division, University of Southern California Medical School, Los Angeles, Calif.

Two operations were performed on his sinuses in 1926 and 1928 without relief. An appendectomy was performed in 1943.

The epigastric pain was of four weeks' duration, was unrelated to meals, and was associated with nausea, vomiting, and some dizziness. He volunteered the information that he was extremely nervous.

Physical examination revealed a well developed man with flushed face, in apparent distress. Breath sounds were prolonged on expiration at both bases, with squeaking rhonchi throughout the entire chest.

Roentgenograms taken in April and August 1947 were reported as showing a definite distortion of the stomach in the prepyloric region consistent with pyloric ulcer with associated spasm. Roentgen-rays taken elsewhere previously were said to have disclosed the presence of an ulcer.

When first seen at the clinic in August the pain and nausea had recurred after an asymptomatic interval under an ulcer therapy regime. A neuropsychiatric consultation was requested at this time, and the impression was that there was an anxiety neurosis present with a possible histaminic cephalalgia. In September he developed urticarial wheals over the face, body and scrotum which persisted after the administration of adrenalin. The gastric symptoms were improved at this time.

Gastroscopy Report (May 20, 1947): No free hydrochloric acid was present in the aspirated gastric fluid. The instrument was passed with ease and much mucus was encountered which at first obstructed the view of the angulus. When a clear view was obtained, a well circumscribed, rather superficial ulcer was seen on the lesser curvature at the angulus, with a whitish base, about 1 centimeter in diameter with a reddish surrounding border. No infiltration was present. The remainder of the body and the cardia of the stomach were well seen and appeared normal.

Impression: Benign peptic ulcer of the anterior wall at the lesser curvature, 2 cm. above the angulus.

Second Gastroscopy (June 10, 1947): The fasting stomach contained 30 c.c. of fluid without free hydrochloric acid. Upon introducing the instrument, the angulus and the antrum were seen immediately, but the pylorus came into view on only one occasion. The formerly observed ulcer could not be seen at this examination. At the onset of the examination the mucosa of the entire stomach appeared normal, but toward the end of the procedure the patient developed an attack of asthma and a remarkable change developed in the gastric mucosa at this point before the eyes of the observer. The folds of the lower portion of the body became markedly swollen. The secretion increased considerably, so much so as to obscure the observation of the greater curvature and parts of the anterior and posterior walls of the stomach. The patient became restless and began to retch and, at this point, further observation of the antrum could not be made.

Impression: Normal stomach gastroscopically at onset of examination, followed by unusual swelling of the mucosa during an attack of asthma.

After removal of the instrument and during the persistence of the attack, the patient developed a sudden and severe headache. Adrenalin given at this point had no effect on the headache.

Third Gastroscopy (September 16, 1947): A controlled experiment was planned at this time. The patient was prepared in the usual manner, special attention being given to the avoidance of undue excitement during the preparation. On this occasion the moment the gastroscope was passed, a severe asthmatic attack began much earlier than the previous one. The instrument was passed with ease and the patient cooperated well. The angulus was immediately seen and during the ensuing five minutes the stomach folds became increasingly reddened and increasing amounts of mucus were secreted. This was thin in consistency and numerous bubbles formed. The folds were then seen to become thicker and edematous. Some swelling was visible in the antrum, but this was not as marked as in the body. One-half c.c. of

1:1000 adrenalin was given subcutaneously and a profound change occurred in two minutes. The swelling decreased markedly, the color of the mucosa reverted to a pale orange-red, and the secretion diminished to a point where we were visualizing a dry stomach. Again a sudden headache appeared following the procedure.

Discussion

Apparently the first reported observations on the gastroscopic appearance of edema of allergic origin were made by René Chevallier in 1935.[1] He reported on transient gastric edema by allergy to bee venom in a bee-keeper who, following bee stings, developed attacks of fainting, urticaria and, 12 hours later, epigastric symptoms simulating pyloric stenosis. At this point gastroscopy revealed transient edema of the antrum which disappeared as clinical improvement occurred.

Pavoit and Chevallier[4] in 1936 discussed, among many cases, one case in which transient edema limited to the antrum and musculus sphincter antri was seen through the gastroscope. This occurred in a young girl who invariably had violent epigastric cramps four hours after the ingestion of milk or eggs; simultaneously she had headache, vomiting, itching of the skin and angioneurotic edema of the eyelids. A similar case was reported by Lundbaek.[7]

The importance of considering transient edema of the stomach as a possible differential diagnosis by roentgen-ray in deformities of the prepyloric area was emphasized by these observers. Pavoit and Chevallier[4] cite 36 cases of this entity with strikingly impressive roentgen-ray studies in which various types, such as the generalized massive type, a massive type involving the lesser curvature, the pseudo-ulcer type, those with total edema of the sphincter antri, the group with partial edema, erosions of the lesser curvature and "fleeting hemorrhages" were classified. In some the edema of allergy closely simulated carcinoma of the stomach.

Some evidence has been presented indicating even more profound and chronic changes in the stomach as a result of an allergic reaction. Paul Chevallier and Moutier,[5] in discussing the stomach in skin diseases, reported gastroscopic findings in eight cases of chronic urticaria and five of angioneurotic edema. In nine, diffuse atrophic gastritis was reported; four were normal. As Schindler points out,[6] it would seem that two things happen: (1) acute transient edema; (2) chronic atrophic gastritis.

More recently, 11 cases of angioneurotic edema of the stomach were observed by Paul Chevallier and F. Moutier (1946).[8] In five, there was massive edema but visceral edema did not invariably coincide with surface edema. Here it was observed that changes occurred from one examination to the next. Afendoulis[9] in 1948 reported three cases of "allergic gastritis," in which the signs were those characterizing chronic "inflammatory" gastritis and emphasized the immediate manifestations of symptoms and the intensity of the process.

It is pertinent to comment that in the majority of the cases reported the involvement seemed confined to the antrum. Our case was significant in that we visualized the edema in the body of the stomach. In the light of the quoted considerations, it would also appear that the superficial ulcer we described in the first gastroscopy may have had an allergic basis.

The relationship of this entity to gastritic changes has been alluded to by Afendoulis and Gulzow[2] who gastroscoped dogs in which anaphylactic shock had

been produced by horse serum injection. Changes appeared in two hours and were marked in nine hours. These consisted of mucosal hemorrhages, reddening, swelling and edema. Microscopic studies suggested the presence of a true gastritis with edema and cellular infiltration. In the future it would seem wise for the gastroscopist to consider allergic edema or allergic gastritis, as well as other forms of gastritis when he encounters bogginess, hyperemia, and hypersecretion of mucus. This gastroscopic impression would be confirmed if, at prolonged and repeated examinations, sudden disappearance of the pathologic findings is observed. It is not yet known whether the amount of eosinophiles in the gastric juice is increased in cases of gastric allergic edema. It may be worth while to investigate this point as a possible useful diagnostic aid. Obviously in such conditions the treatment must hinge upon the allergic etiology. Antihistaminic drugs may be tried.

Summary

A case of bronchial asthma is reported in which gastroscopy acted as a trigger mechanism for the production of attacks of asthma.

Transient gastric edema of the body of the stomach was observed through the gastroscope simultaneously with the attacks. This phenomenon cleared, at one observation, following the use of adrenalin.

In the future the internist, the roentgenologist and the gastroscopist have an added responsibility in this respect.

The roentgenologist should be more alert to and include this condition in the differential diagnosis of roentgen-ray defects of the body and antrum of the stomach.

The gastroscopist should consider allergy as a possible cause of gastritic changes based on gastroscopic criteria as outlined above.

The clinician should include allergy of the stomach in his list of possible causes of the ulcer-symptom complex, and should not fail to delve into the allergic history with this relationship in mind.

BIBLIOGRAPHY

1. Chevallier, R.: Oedeme gastrique fugace par allergie au venin d'abeille, Compt. rend. Soc. de biol. de Lyon **109**: 203, 1935.
2. Afendoulis, T. C., and Gulzow, M.: Allergisch-hyperergische Gastritis, Ztschr. f. d. ges. exper. Med. **104**: 167, 1938.
3. Pollard, H. M., and Stuart, G. J.: Experimental reproduction of gastric allergy in human beings with controlled observations on mucosa, J. Allergy **13**: 467, 1942.
4. Pavoit, J., and Chevallier, Rene: Les gastropathies allergiques, J. d. méd. de Lyon, p. 31, 1936.
5. Chevallier, Paul, and Moutier, F.: L'estomac dans les maladies de la peau, Rev. d. path. comparée **470**: 1325, 1935.
6. Schindler, R.: Gastritis, 1947, Grune and Stratton, New York.
7. Lundbaek: Et tilfaelde af gastroscoisk veriferet ventrikelodem ved, Quincke's Sygdom. Ugesk. f. Laeger **22**: 658, 1939.
8. Chevallier, Paul, and Moutier, F.: Angioneurotic edema of the stomach, Presse méd. **54**: 860, 1946.
9. Afendoulis, T. C.: Observations on acute allergic gastritis, Am. J. Digest. Dis. **15**: 90, 1948.
10. Friesen, S. R., State, D., Jasper, D. E., et al.: Production of allergic gastric and duodenal edema which predisposes to histamine-provoked ulcer in dogs, Surgery **23**: 167, 1948.

THE RENAL PERISTALTIC CYCLE AND NEUROMUSCULAR ASPECTS OF RENAL FUNCTION AND THEIR RELATIONSHIP TO DISEASES OF THE KIDNEY *

By BERNARD HATZ, B.Chem., M.D., *Peekskill, New York*

THE neuromuscular apparatus of the kidney and its functions in health and in disease have been too long neglected. It has been known for at least 80 years that the ureter exhibits peristaltic waves. Howell in his Textbook of Physiology refers to a study by Engelmann published in Pfluger's Archives in 1869. Keyes [9] speaks of the emission of a little jet of urine from the ureter as "perhaps the most picturesque phenomenon observable through the cystoscope." It is not so well known that the kidney calyces themselves exhibit rhythmic peristaltic activity. If they did not, the lower calyces would soon stagnate. Yet, the literature shows relatively little application of this physiological knowledge to that of pathology. It is the purpose of the present paper, with the aid of an illustrative case, to focus attention on this phase of renal excretory function, since the author feels that by its neglect, important clinical aspects of kidney disease have been missed, and that vice versa, with greater awareness and attention to these aspects of urine excretion, a more accurate and fuller understanding will be applied to conditions hitherto little understood. Furthermore, as demonstrated in the case to be reported, the renal peristaltic cycle is a field of clinical physiology and pathology in which roentgenology can be expected to make important direct primary contributions. There remains much to be done since the information we have is scanty at best.

The calyces and pelvis of the kidney together with the ureter constitute a hollow viscus, possessed of a muscular coat, with longitudinal and circular layers,[1, 9] and functioning with rhythmic systolic and diastolic movements as will be pointed out, subject to control by the autonomic nervous system. The pelvis and calyces and ureter are thus not just a simple collecting conduit system by which the urine reaches the bladder,—with a funnel arrangement in the kidney, ending in a long ureteral stem to the bladder, the ureter being granted some peristaltic activity. Muschat [8] graphically describes observations in an operative case of "powerful contractions of a large extrarenal human pelvis in situ, appearing every 15 to 20 seconds and lasting for seconds at a time. We saw systole and diastole at regular intervals without interruption."

The circular muscle fibers described above are concentrated at certain points in such a manner as to form a system of sphincters or minute muscular contractile tubes which connect the separate chambers with each other. This sphincter or ring-muscle system has been variously described in different degrees of detail by a number of urologists and investigators, among whom Kelly and Burnam,[2] Narath [3] and Muschat [4] have given good descriptions. The sphincters occur at the point of insertion of papilla in the cupped end of the minor calyces; at the point of entry from the minor calyx into the major calyx; at the

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point where the major calyx enters the pelvis; and finally at the uretero-pelvic junction. They thus form a series of sphincters or muscular contractile tubes connecting tubules with calyces, calyces with pelvis and finally pelvis with the ureter.

Pyeloscopic and pyelographic observations made with serial radiographs [5] show the calyces to contract in succession from above downwards, the contraction starting in the uppermost calyx where the pyramid is attached. As soon as the superior calyx contracts, the sphincter at its neck relaxes, permitting the calyceal contents to be expelled into the pelvis. At the completion of this systole, the sphincter contracts, preventing regurgitation from the pelvis into the calyx. The next lower calyx then contracts and another cycle begins. As the lowermost calyceal systole is finished, the pelvis contracts, propagating its contents into the ureter, thus initiating a peristaltic wave in the latter, which is transmitted down into the bladder.

We have thus a hollow viscus consisting of several muscular chambers, contracting in a definite sequence, very reminiscent of the blood flow through the heart as Jona [5] has pointed out. Further, the pelvis exhibits a maintenance filling, never quite emptying completely, paralleling the phenomenon described in the heart. Thus 8 to 12 contractions of the pelvis can be seen before the diluted radiopaque substance can no longer be seen in the pyelographic study.[5] We have thus a demonstration of the phenomenon of tone.

The principle of reciprocal innervation of muscles is also demonstrated here as in any other hollow viscus. The contractions of the calyces, or pelvis, proceed pari passu with a relaxation of the respective ring-muscle sphincter or connecting tubes. Harris [6] has demonstrated vigorous pelvic and calyceal contractions following the intramuscular injection of eserine. Jona,[5] too, has confirmed these effects of cholinergic stimulation. The motor nerve supply of the calyx and pelvis appears to be derived from the vagus; the sphincter system is reciprocally innervated by the sympathetic.

The normal renal peristaltic cycle then, exhibits a definite sequence of contracting chambers, following the physiological pattern of any hollow viscus including manifestations of tone and reciprocal innervation. Any disturbance of this cycle can result in a neuromuscular dysfunction, which can produce a clinical picture, consisting of loin pain and symptoms of an obstructive nephropathy, based physiologically on a dyskinesia resulting in spasms, dilatations and atony, stasis and eventual hydronephrosis.

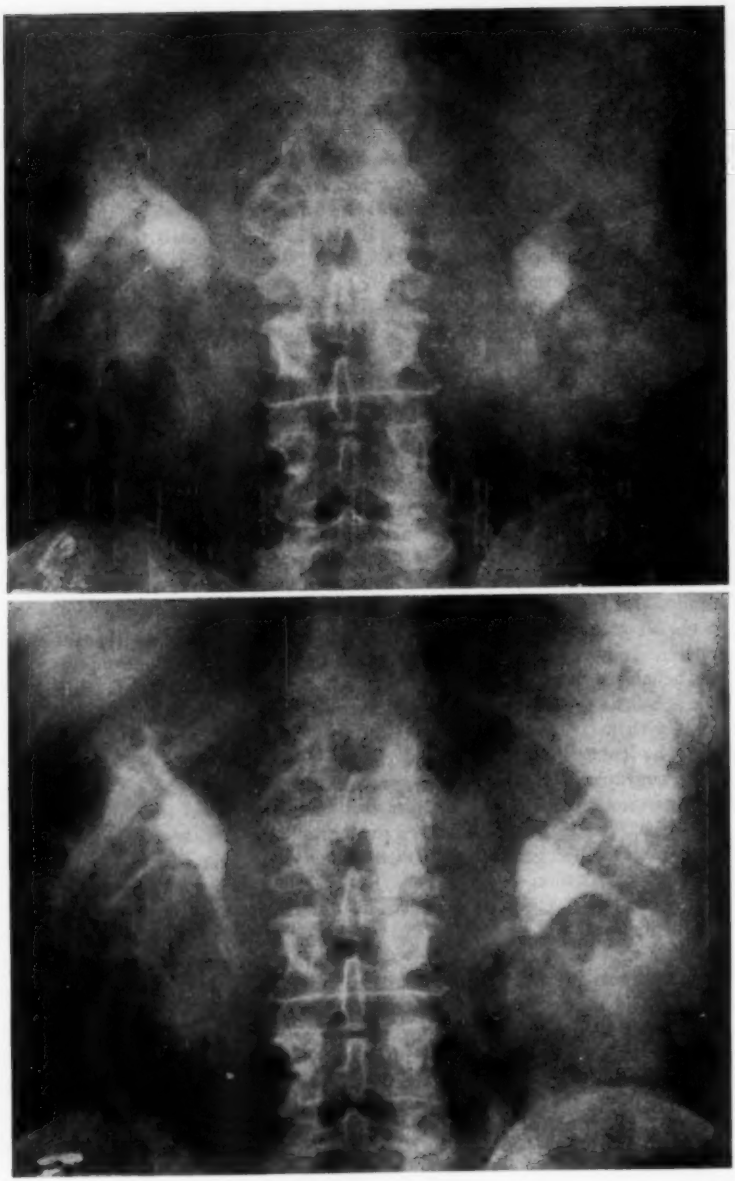
The dysfunction may involve a disturbance of the principle of reciprocal innervation, with a sphincter spasm which is not unlike the conditions seen in cardiospasm of the esophagus or Hirschsprung's disease of the colon. Thus, such an achalasia or sphincter spasm results in calyceal and pelvic stasis, with ensuing dilatation and an eventual hydronephrosis which exists without evidence of organic obstruction. Such cases have been described by Harris [6] under the term of "renal sympatheticotonia," which he has dramatically relieved by renal sympathectomy. The autonomic imbalance resulting in a sympathetic preponderance may not only be due to a primary renal sympatheticotonia, but may be a reflex secondary to afferent impulses from a distant diseased focus, as in a cholecystitis.[5] Jona reports a complete restitution to normal, following a cholecystectomy, of a previously disturbed cycle with a "pyelitis" syndrome and

demonstration of an hydronephrosis. On the other hand, there are transient disturbances, "formes frustes" of neuromuscular dysfunction which are amenable to therapy before the stage of stasis and eventual hydronephrosis with the production of an obstructive nephropathy, has had an opportunity to become clinically fixed. Thus Jona [5] has demonstrated the interesting fact that not infrequently there is an abnormal peristaltic cycle in certain dysfunction cases of "pyelitis" in pregnancy. With the use of pituitrin, he has initiated a normal peristaltic cycle which tends to continue with a complete restoration of normal function and a disappearance of the acute and alarming symptomatology. Again, infection or any local unphysiologic or pathologic condition such as a small tumor, may result in an altered renal peristalsis. Thus, in a pyelitis, there may be a spastic pelvis, more or less permanently contracted calyceal and pelvic sphincters, and a disordered peristalsis, which will disappear if the infection has not been too severe or long-continued. Here, the spasm of the pelvis and calyces may be compared to the spasm and irritability of the duodenal bulb when the latter is the seat of inflammatory changes. Keyes [7] agrees with Jarre and Cumming who described sphincter spasm and altered renal peristalsis at the International Urological Congress of 1936, stating that altered, "partial or reversed waves are unusual except as the result of trauma or disease."

There is nevertheless, a syndrome of continued neuromuscular dysfunction, resulting in an achalasia of the sphincters, causing calyceal and pelvic stasis, eventual hydronephrosis and an obstructive nephropathy associated with a definite clinical syndrome which Harris [6] has described under the term of renal sympatheticotonia. The dysfunction is usually unilateral, associated with kidney or loin pain, and costovertebral tenderness, and presenting no demonstrable organic cause of obstruction. Eserine characteristically relieves the spasm with strong pelvic and calyceal contractions but after its action is terminated, the sphincter achalasia recurs. Harris performs a renal sympathectomy with a relief of the achalasia and disturbed peristaltic cycle and, where the condition is still reversible, with an eventual restoration to completely normal physiology and relief of the hydronephrosis.

Roentgenographically, three stages may be demonstrated [6]: (1) A stage of irritability of systole showing a small or contracted pelvis on the one side with evidence of delayed emptying. Here, pyelographic observations will demonstrate that eserine injection results in emptying the pelvis with relief of pain. (2) Stage of exhaustion or diastole. The pelvis is now enlarged, but still capable of contraction. (3) Stage of paralysis with long continued stasis, atony, and hydronephrosis.

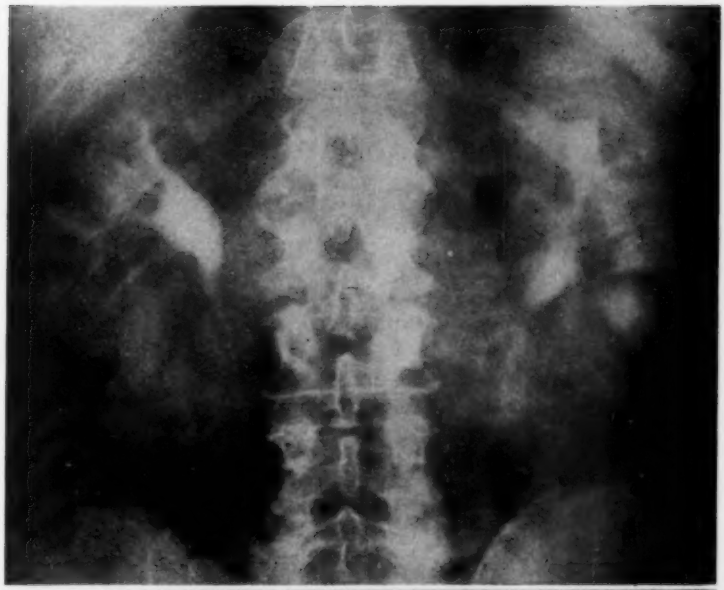
The following case presents a series of films in an intravenous urogram study, which demonstrates in principle the neuromuscular dysfunction described in detail above. It is interesting that this case exhibits, in addition to evidence of a dyskinetic peristaltic cycle that appears on one side only, a past history of hematuria, a urologic consultation with cystoscopic studies, revealing no organic pathology. More interesting is the presence of a hypertension, which raises the possibility that a long continued dyskinesia and sphincter spasm may produce an obstructive nephropathy with a resultant hypertension on the Goldblatt kidney basis. It may be that the dyskinesia is associated with renal artery spasm. The unilateral dyskinesia and altered peristaltic cycle are demonstrated on



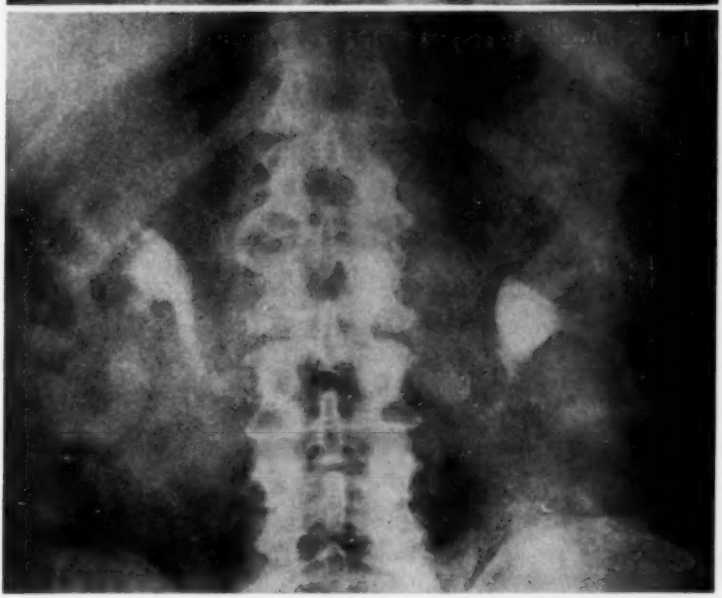
A

B

FIG. 1. A and B.

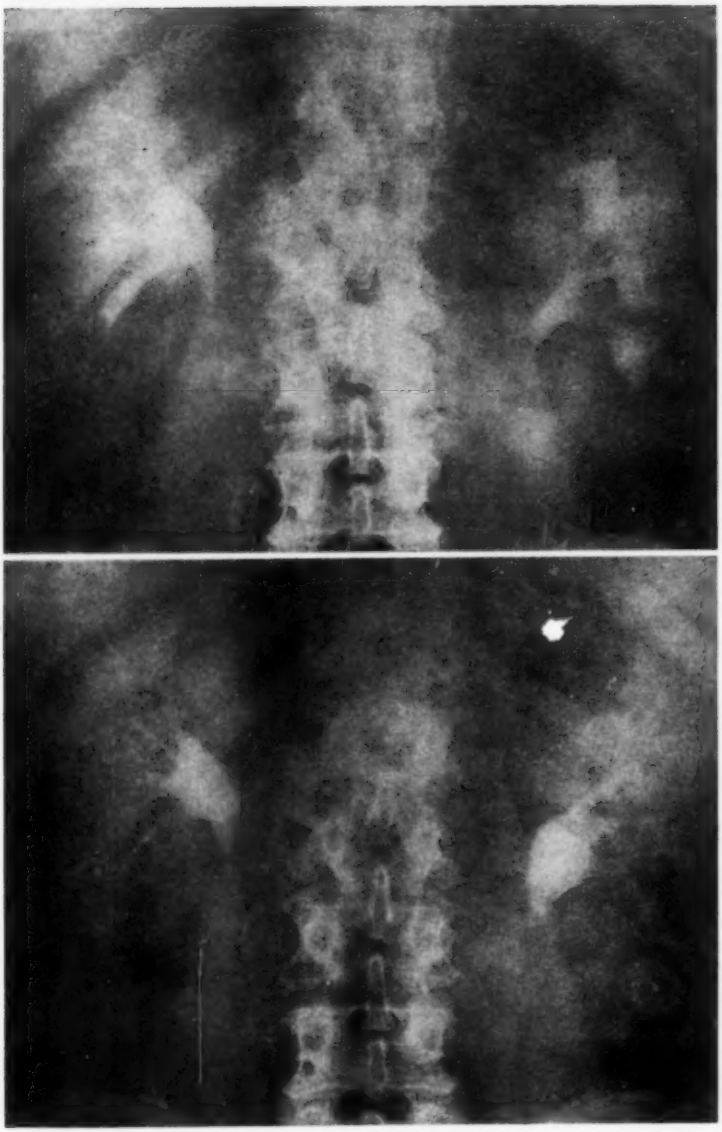


C



D

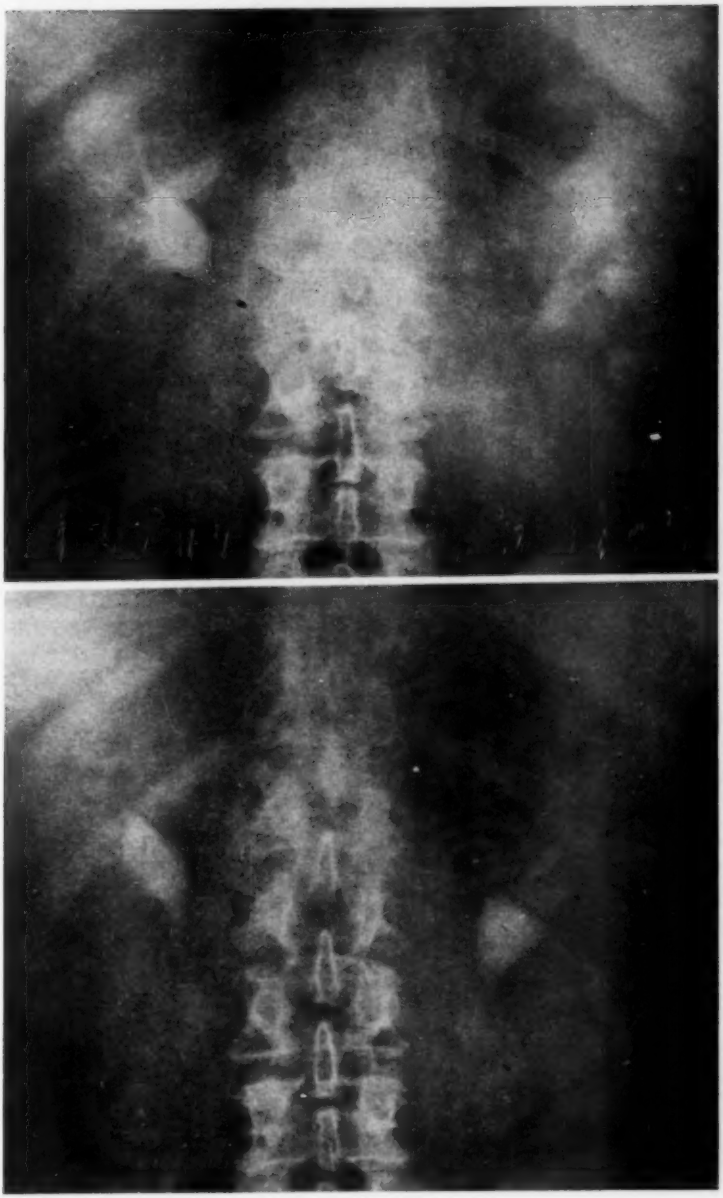
FIG. 1. C and D. Excretory urogram with films taken at 5, 10, 15 and 30 minute intervals after administration of dye. This series shows on the 15 minute film (C) a complete dyskinetic disorder in the left kidney with spastic pelvis and calyces and the dye as far back as the papillae collected in great globs of density. Note the sphincter spasm at the ureteropelvic junction, demonstrated by a negative shadow. Also note the restoration to the "normal" for that side on the next film of 30 minutes. The right side is normal throughout.



A

B

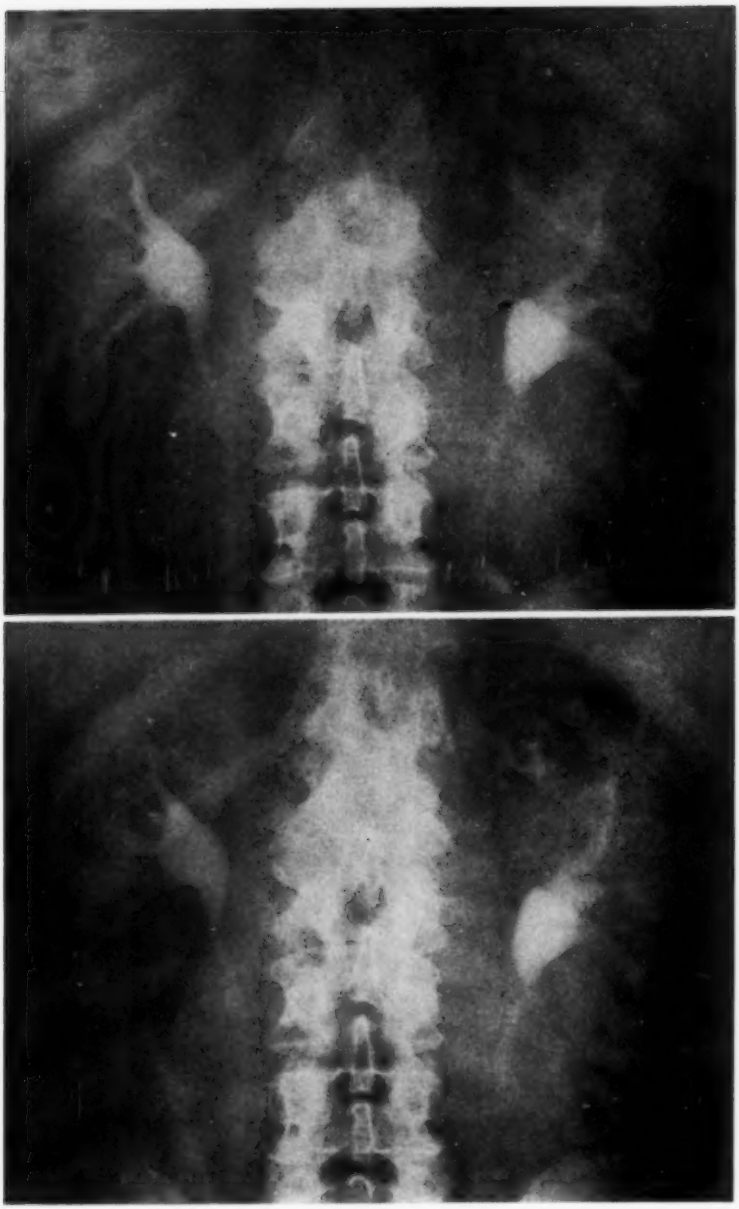
FIG. 2. A and B.



C

D

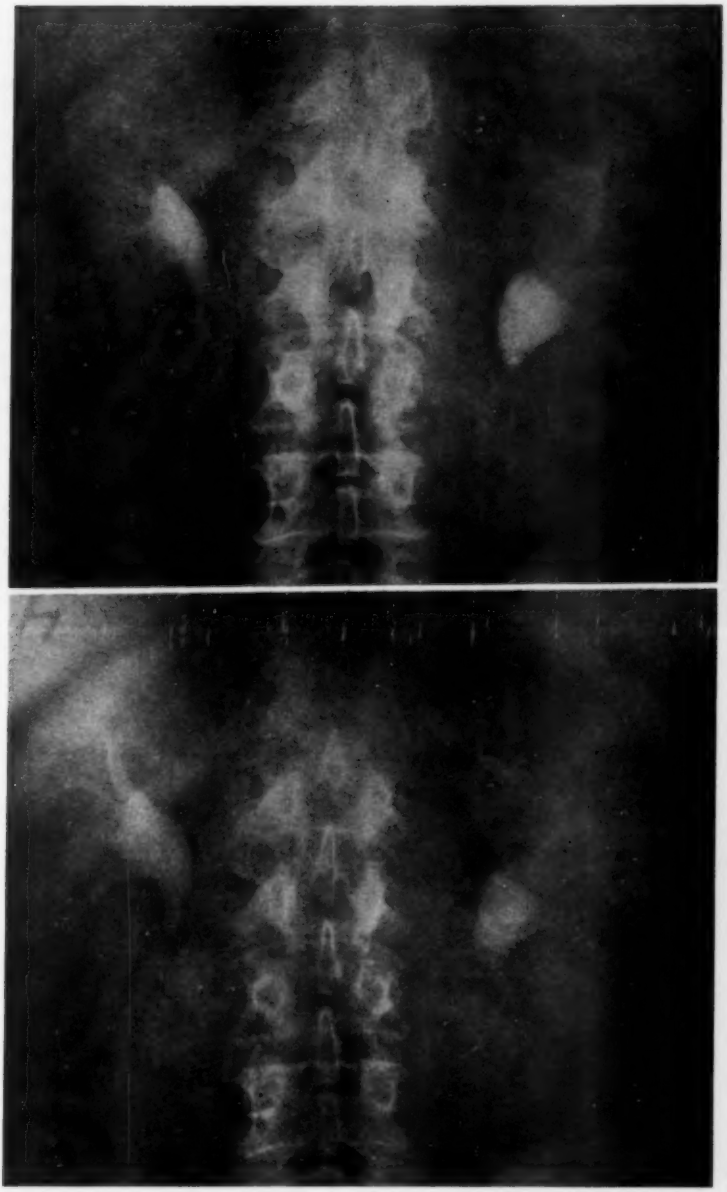
FIG. 2. C and D.



E

F

FIG. 2. E and F.



G

H

FIG. 2. G and H. Second excretory urogram taken three and one-half months later with films at 5 minute intervals during an hour's observation. The eight parts to figure 2 represent the first 40 minutes. Again the gross dyskinesia is noted on the left, this time on the 5 minute (A) and 15 minute (C) films. Following each dyskinetic episode, a restoration to "normal" is noted, which after the 15 minute film was carried to the 45 minute film, which is shown in figure 3. The right side remains normal throughout.

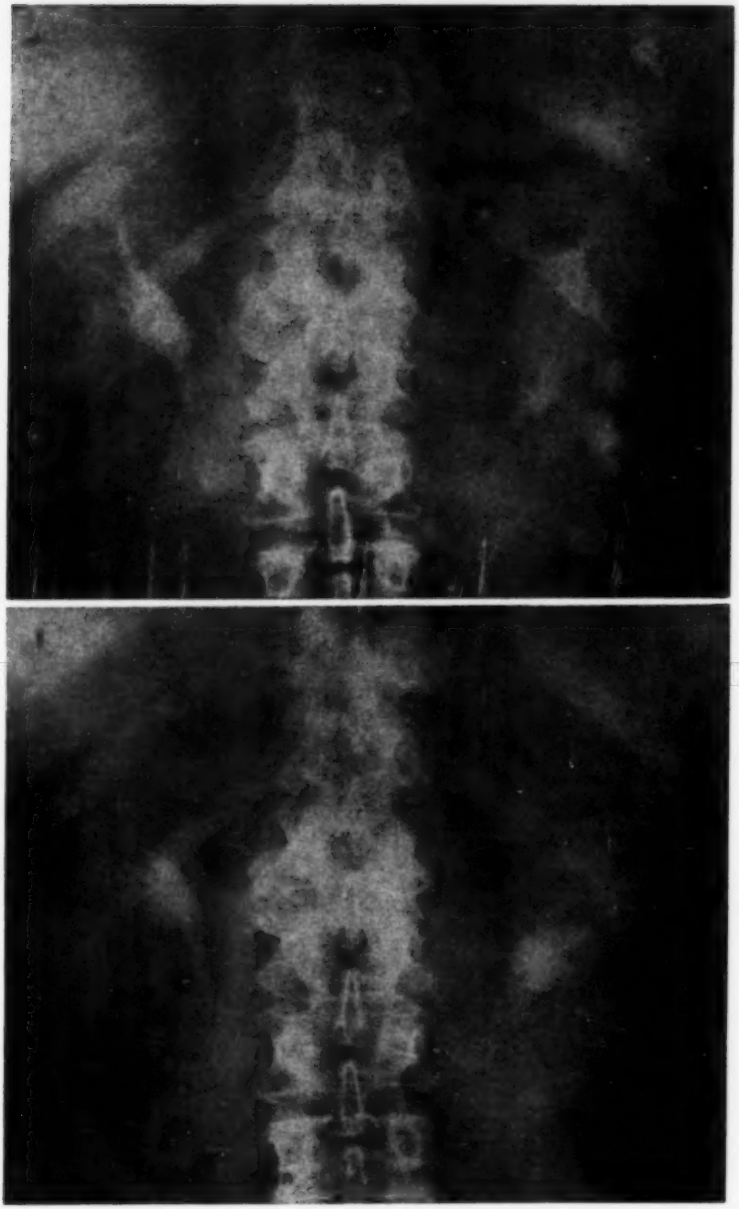


FIG. 3. A and B. Continuation of previous cycle, with a recurrence of the spasm of the pelvis and calyces and picture of dyskinesia at 45 minutes (A) and return to "normal" at 50 minutes (B).

intravenous urograms on two occasions, being first noted December 13, 1948, and beautifully confirmed three and a half months later on March 29, 1949, thus demonstrating a persistent neuromuscular dysfunction. The second study shows calyceal and pelvis visualization every five minutes. The five, 15 and 45 minute films demonstrate the recurring disturbed peristaltic cycle. A series of normal studies taken at such intervals fails to reveal any such peristaltic alterations throughout the periods of their observations. As stated at the beginning of this paper, these findings indicate a direction for further investigation and studies of the renal peristaltic cycle. More serialographic studies at shorter intervals to include the rhythmic events described by Muschat [8] should reveal important roentgen data. We are at present engaged in a series of intravenous urogram studies with observations at two to three minute intervals, subjecting those cases demonstrating spastic states, to further study under conditions of adrenergic blockade.

Case Report

A 54 year old white male complained of back pain and an episode of hematuria. The patient was treated in an out-patient ambulatory clinic. The physical examination was essentially negative except for a hypertension of 150/100 mm. Hg. The urine showed occasional red blood cells, and a few leukocytes, but otherwise was normal. Cystoscopy revealed no lesions of the urinary tract to account for the hematuria. Excretory urograms taken on December 13, 1948 (figure 1) showed a slightly enlarged kidney on the left. The transportation of the dye was rapid and normal on both sides, and the upper collecting systems were visualized well on both sides without significant abnormalities, other than a suggestive minimal hydronephrosis on the left. These findings are nicely demonstrated on a five and 10 minute film after the administration of dye, but on the 15 minute film a change takes place on the left side showing marked dilatation of the calyces and pyramidal areas with retrograde flow of the dye. At the same time, the pelvis shows contraction, and a negative sphincter spasm shadow is observed at the ureteropelvic junction. On the 30 minute film, the normal calyceal and pelvic pattern is restored on the left side. The impression at the time was that we were dealing here with a probable disturbed renal peristaltic cycle demonstration. A simple pyelorenal backflow was not considered contributory since we had no overdistention or other factors as one might have in a retrograde study.

Accordingly, the patient had another intravenous urogram study (figures 2 and 3) performed on March 29, 1949, three and a half months after the first study. This time, attempts at peristaltic cycle study were made with films at five minute intervals throughout a 60 minute period and three excellent demonstrations of the dyskinesia discussed, were obtained as will be seen on the five, 15 and 45 minute observations.

Summary and Conclusions

1. The renal peristaltic cycle is a field of clinical physiology and pathology in which roentgenology can be expected to make important direct contributions. It is an area of kidney function which has been too long neglected and which can contribute much to a better understanding of non-nephritic kidney conditions.

2. The neuromuscular apparatus of the kidney involved in this peristaltic aspect of kidney function rests in the calyces and pelvis which, together with the ureter, form a hollow viscus possessing muscular layers with a sphincter system and which function with a rhythmic systolic and diastolic sequence, subject to control by the autonomic nervous system.

3. The normal rhythmic cycle is described.

4. The peristaltic cycle is subject to disturbances and dyskinesias, altered as a result of trauma, infection or disease, to include even early tiny tumor foci, within the calyx-pelvis, ureter ensemble, or as a result of autonomic imbalance. An irritable, spastic pelvis and calyces in pyelitis are described, similar to duodenal bulb irritability in inflammatory lesions of the duodenum.

5. A renal sympatheticotonia is described with sphincter spasm, comparable to the achalasia or cardiospasm of the esophagus, or in Hirschsprung's disease of the colon, resulting in the kidney in severe spasms, pelvic and calyceal dilatations, and stasis, and eventual atony and hydronephrosis if sufficiently long prolonged.

6. Such obstructive nephropathies, existing without evidence of organic obstructions, are associated with a clinical syndrome, and may even underlie certain types of hypertension.

7. Relief by renal sympathectomy or by other means as by drugs with autonomic action is discussed.

8. A series of films is presented to illustrate the conditions described.

BIBLIOGRAPHY

1. Gray, H.: Anatomy of the human body, 24th Ed., 1942, Lea and Febiger, Philadelphia, p. 1246.
2. Kelly, H. A., and Burnam, C. F.: Diseases of kidneys, ureters and bladder, 1914, D. Appleton & Co., N. Y., Vol. 1, p. 167.
3. Narath, P. A.: The hydromechanics of the calyx renalis, J. Urol. **43**: 145–176, 1940.
4. Muschat, M.: Musculus spiralis papillae, J. Urol. **16**: 351, 1926.
5. Jona, J. L.: The kidney pelvis, Proc. Royal Soc. Med. **29**: 623, 1936.
6. Harris, S. H.: Renal sympathectomy, Proc. Royal Soc. Med. **28**: 1497, 1935.
7. Keyes, E. L., and Ferguson, R. S.: Urology, 1936, Appleton-Century Co., N. Y.
8. Muschat, M.: Hypertrophy of the spiral muscle of the renal papillae, Ann. Surg. **109**: 151–155, 1939.
9. Keyes, E. L.: Textbook of urology, 1924, D. Appleton and Co., Philadelphia, p. 415.

Q FEVER: REPORT OF A CASE TREATED WITH CHLOROMYCETIN *

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IT IS of interest that Q fever is being encountered with increasing frequency in the United States.[1, 2, 3, 4] Furthermore, it is now evident that this rickettsial infection may give rise to severe clinical disease, especially in older individuals. Indeed, at least four fatalities have been ascribed to this disorder in this country alone.[5] The need for a satisfactory form of therapy is therefore apparent. In this connection, Wong and Cox have demonstrated the effectiveness of aureomycin in the disease produced experimentally.[6] More recently, Lennette and

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his associates [7] evaluated aureomycin in a clinical trial and found it to be beneficial in patients with this condition.

The purpose of this report is to present the results of therapy of an isolated case of Q fever with another antibiotic, namely, chloromycetin. That chloromycetin might also be of value in the disease was inferred from the knowledge that this compound is generally effective in other rickettsial infections.[8] The case reported herein is of additional interest in that the exact date of exposure to infection is known.

Case Report

A 43 year old Danish physician was admitted to the University Hospital on November 22, 1948, with complaints of chills, fever, severe headache, and malaise. He had been visiting various laboratories in this country for nine weeks prior to admission. On October 29, 1948, the patient had gone to the research laboratories of the

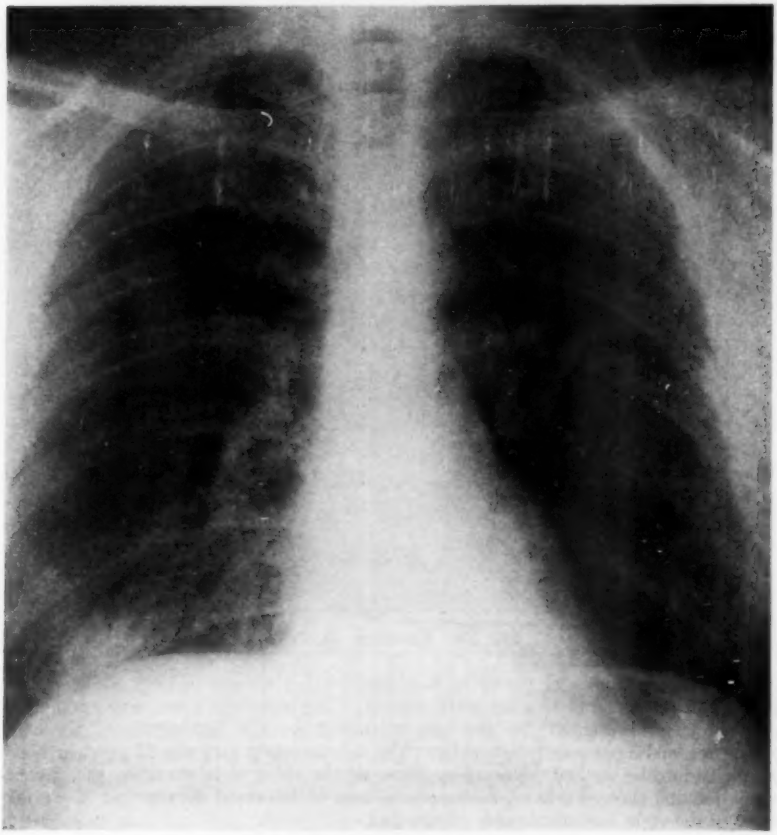

Fig. 1 *a*. November 22, 1948.

National Institutes of Health at Bethesda, Maryland. The visit included a brief stop at the section engaged in work with Q fever. Following this, he remained well until November 20 when he felt hot and tired. That night, headache and chills were first experienced and the patient slept poorly. These symptoms persisted and he felt extremely fatigued. A dry, hacking cough appeared and a feeling of nausea was present on the day of admission, two days after onset.

Physical examination revealed the temperature to be 103.8° F., the pulse 100, and respirations 25 per minute. The blood pressure was 140 mm. Hg systolic and 70 mm. Hg diastolic. The patient appeared febrile, but his general appearance was better than the high fever would indicate. The skin was hot and moist. Examination of the chest failed to reveal any abnormalities, and the remainder of the physical examination was negative.

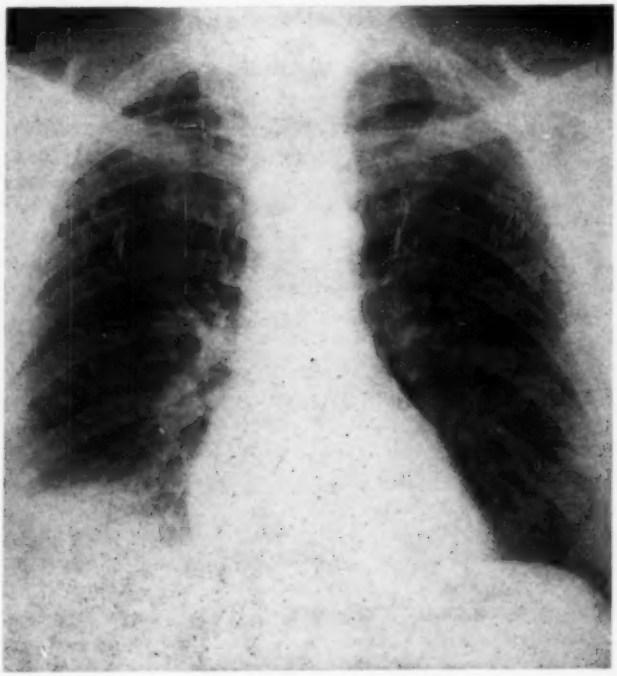

FIG. 1 *b*. November 26, 1948.

Laboratory studies of the urine and stool yielded normal findings. The hemoglobin and red blood cell values were normal. The leukocyte count was 7,800 with the following differential: 80 per cent polymorphonuclear leukocytes, 17 per cent monocytes, and 3 per cent lymphocytes. The sedimentation rate was 33 mm. per hour by the Wintrobe method. Roentgenograms of the chest were made on the day of admission and showed a hazy, homogeneous area of increased density just above the dome of the right hemidiaphragm (figure 1a).

During the first 24 hours of hospitalization the patient received 0.65 gram of

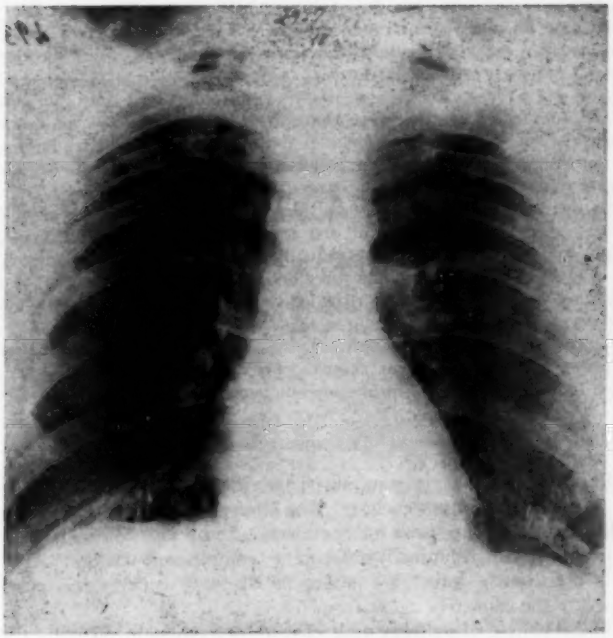

FIG. 1 c. December 21, 1948.

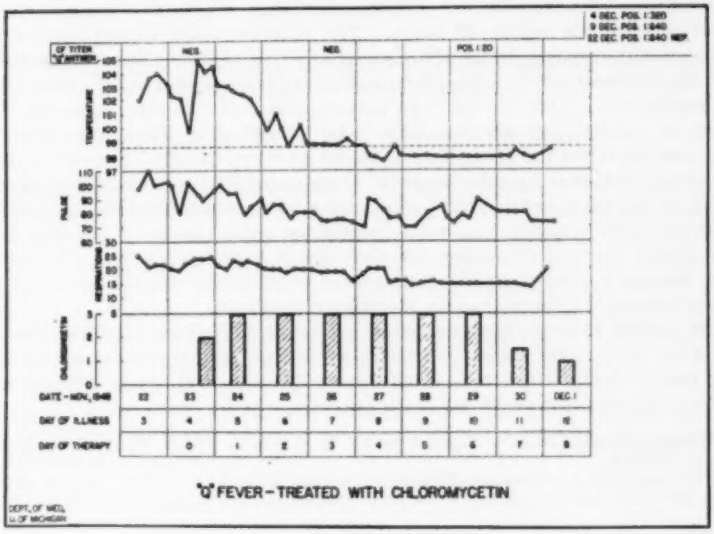

FIG. 2.

aspirin on three occasions, the last dose being at 3:00 p.m. on November 23. At 9:30 p.m. on that date he received an initial dose of 2.0 grams of chloromycetin,* orally, and 1.0 gram every eight hours thereafter until November 29, when the dosage was reduced to 0.5 gram at the same intervals.

Vomiting occurred twice during the first hospital day. On the morning of November 24, fine transient râles were heard at the right lung base, posteriorly. On this date the patient failed to experience chills and he felt somewhat improved. By the following evening, he was afebrile and had no complaints except for some weakness and ease of fatigue. He was discharged on December 1, 1948.

During the patient's illness and convalescence, frequent chest roentgenograms were taken. At first, progression of the infiltrative pulmonary lesion was noted (figure 1b). The pneumonitis then gradually regressed but a residual area of involvement was still evident one month after onset of illness (figure 1c). A check-up examination some two months later revealed, however, that the process had cleared completely.

In the accompanying chart (figure 2), the hospital record of the patient's temperature, pulse, and respirations is shown. The amount of chloromycetin administered is also indicated as are the results of complement-fixation tests for Q fever.†

Discussion

The diagnosis of Q fever was suspected in this case from the history of exposure to infection 22 days earlier. The clinical and laboratory findings were compatible with those described for the disease.[9] Later, the diagnosis was confirmed by the results obtained in specific complement-fixation tests. Since Q fever is notoriously infectious among laboratory workers, no attempt was made to isolate the causative agent from the patient.

The clinical course of patients with Q fever is extremely variable. Robbins [9] found an average duration of fever of seven to eight days, with extremes of one to 15 days. Chloromycetin therapy was instituted in this case at the beginning of the fourth 24 hours of illness. Improvement was evident in 18 hours and the patient was afebrile within 48 hours. The observed improvement cannot be attributed with certainty to the chloromycetin. It is believed, however, that the rapid improvement which followed therapy is at least suggestive. Further trial of chloromycetin in Q fever, therefore, appears indicated. In this connection, the studies of Smadel and his associates [10] are of interest. These investigators found that the rickettsial agent responsible for Q fever, namely, *Coxiella burneti*, is relatively resistant to chloromycetin when compared with other rickettsiae. Indeed, in experimentally infected chick embryos, it was noted that the amount of chloromycetin required to produce significant prolongation of life was four times greater for *C. burneti* than for the other rickettsial organisms. It seems likely, therefore, that comparably larger doses of chloromycetin will be necessary in clinical cases of Q fever than for the other rickettsioses.

The patient reported herein received a total of 22.5 grams of chloromycetin over nine days. This appears to have been adequate and may represent the lower limit of dosage required to be effective in Q fever on the basis of the above-indicated findings of Smadel and his colleagues.

* Kindly supplied for use in this case by Dr. E. C. Vonder Heide, Parke, Davis & Co., Detroit, Michigan.

† Performed by the Virus and Rickettsial Division of the Army Medical School, Washington, D. C., through the courtesy of Dr. J. E. Smadel.

SUMMARY

A case of Q fever, developing 22 days after a single exposure, was treated with chloromycetin. An apparently favorable therapeutic result was achieved, and it is concluded that further trials of chloromycetin in Q fever are warranted.

BIBLIOGRAPHY

1. Topping, N. H., Shepard, C. C., and Irons, J. W.: Q fever in the United States. I. Epidemiological studies of an outbreak among stock handlers and slaughterhouse workers, J. A. M. A. **133**: 813–815, 1947.
2. Shepard, C. C.: An outbreak of Q fever in a Chicago packing house, Am. J. Hyg. **46**: 185–192, 1947.
3. Shepard, C. C., and Huebner, R. J.: Q fever in Los Angeles County. Description of some of its epidemiological features, Am. J. Pub. Health **38**: 781–788, 1948.
4. Janton, O. H., Bondie, A., Jr., and Sigel, M. M.: Q fever. Report of case in Pennsylvania, Ann. Int. Med. **30**: 180–184, 1949.
5. Brown, D. C., Knight, L. A., and Jellison, W. L.: A fatal case of Q fever in Southern California, California Med. **69**: 1948.
6. Wong, S. C., and Cox, H. R.: Action of aureomycin against experimental rickettsial and viral infections, Ann. New York Acad. Sc. **51**: 290–305, 1948.
7. Lennette, E. H., Meiklejohn, G., and Thelen, H. M.: Treatment of Q fever in man with aureomycin, Ann. New York Acad. Sc. **51**: 331–342, 1948.
8. Smadel, J. E., and Jackson, E. B.: Chloromycetin, an antibiotic with chemotherapeutic activity in experimental rickettsial and viral infections, Science **106**: 418–419, 1947.
9. Robbins, F. C.: Q fever, clinical features. The rickettsial diseases of man, Am. Ass. Adv. Sc., 1948, pp. 160–168, Washington, D. C.
10. Smadel, J. E., Jackson, E. B., and Cruise, A. B.: Chloromycetin in experimental rickettsial infections, J. Immunol. In press.

TRAUMATIC THROMBOPHLEBITIS DURING INTRA-ARTERIAL HISTAMINE THERAPY *

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THE purpose of this presentation is to report a complication observed while giving histamine intra-arterially in the treatment of peripheral vascular disease. The treatment of obliterative arterial disease described by Mufson [1] has a definite appeal because it may be done as an office procedure. Before this method of therapy was suggested, there was little that could be offered the patient with obliterative arterial disease except in larger centers where long periods of treatment on Saunder's bed, sympathectomy, or physical therapy could be given. Such regimes of therapy are frequently so costly as to be beyond the reach of many patients who need therapy of a definitive type.

Because of the great number of patients who will probably be receiving this type of therapy, we would like to report a complication observed while giving histamine intra-arterially.

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Case Report

A 67 year old retired farmer presented himself to the clinic on January 13, 1949. His presenting complaint was pain and paresthesias in his right leg of two years' duration. A diagnosis of arteriosclerosis obliterans was made. Intra-arterial histamine was administered after the fashion outlined by Mufson and for the first five such treatments little difficulty was encountered. During the sixth intra-arterial histamine treatment, however, considerable difficulty was encountered in getting the needle into the femoral artery. It was only after several attempts and considerable trauma that the femoral artery was entered. After the treatment was completed it was noted that there was a purple mottling to the skin of the affected extremity extending from the knee distally. The veins were distended. However, on elevation they collapsed quickly. The patient did not complain of pain. He was dismissed from the office and he went home where he spent a comfortable evening. The next morning he noted swelling of the right leg below the knee. The next day he returned to the office because of the increase in the size of the limb. At this time there was pitting edema extending up to the knee which was graded II plus on the basis of IV. Calf tenderness was noted. There was no femoral triangle tenderness. The Homan sign was negative. It was our impression that the patient was suffering from deep femoral thrombophlebitis probably of a post-traumatic nature. We felt that the wall of the femoral vein had been subjected to considerable trauma during the attempts at puncturing the femoral artery and that a thrombus formed at the site of the intimal trauma. The patient was hospitalized and routine anti-coagulation therapy initiated. The leg was elevated and warm packs were applied. After five days of this regime the swelling in the legs subsided and no further complications were encountered. To date there has been no further evidence of thrombo-embolic disease.

Discussion

We have presented a patient with arteriosclerosis obliterans who we feel developed a traumatic thrombophlebitis during the time he was receiving intra-arterial histamine therapy. To our knowledge there have been no previous reports of complications following this type of therapy. Because of the probable wide usage of this type of treatment in the future we feel complications of this nature should be reported.

BIBLIOGRAPHY

1. Mufson, Isador: A new treatment for the relief of obliterative disease of peripheral arteries, Ann. Int. Med. 29: 903, 1948.

EDITORIAL

THE DIETETIC TREATMENT OF HYPERTENSION AND NEPHRITIS

MANY therapeutic procedures for the relief of hypertension, dietetic, medicinal and surgical, have been proposed during the past 50 years. When advocated with sufficient vigor and authority and supported by statistical evidence which seemed imposing, many of these have stimulated wide spread interest which has gradually waned as the results in practice fell far short of the expectations which had been aroused. At present we are near—probably a little past—the crest of a new wave of enthusiasm which followed the report of Kempner [1] of the successful use of a "rice-fruit-sugar diet" for the treatment of nephritis and hypertension. A current evaluation of this work, even if only tentative and incomplete, would seem to be of value.

In either evaluating or attempting to confirm this work it is essential to bear in mind that the procedure is still really on an almost purely empirical basis. The therapeutic value of the rice diet must be determined by adequate clinical trials, quite regardless of the validity of either the working hypothesis on which Kempner originally based his experiment [2] or the current explanations of how and why the diet "works."

Attempts to influence hypertension by restricting the intake of sodium chloride ("dechloruration") were reported by Achard and by Widal in the early part of this century. Their results were not impressive. In this country interest was first aroused by the work of Allen and associates (1920, 1922) [3] who reported a study of 180 hypertensive patients kept for long periods on a diet containing from 0.5 to 0.75 gm. of salt per day but adequate in caloric and protein content. Improvement was judged by a fall in blood pressure and relief of subjective discomforts. In about 60 per cent of his patients either the blood pressure dropped to normal or there was "distinct benefit." Undoubtedly a significant number of Allen's patients were benefited. His reports were not convincing, however, because his criteria of improvement were not adequately specified and because there was virtually no preliminary control period to show how marked were spontaneous variations in blood pressure, independent of the diet.

Many attempts to repeat this work were subsequently reported with widely conflicting but usually disappointing results. Many of these studies, however, were also unsatisfactory in that the series was often too small, the period of treatment too short, preliminary control periods inadequate or the degree of salt restriction not sufficiently rigid. The diet was not palatable

[1] Kempner, W.: The treatment of kidney disease and hypertensive vascular disease with rice diet, North Carolina M. J. **5**: 125–131, 1944.

[2] Kempner, W.: Compensation of renal metabolic dysfunction. Treatment of kidney disease and hypertensive vascular disease with rice diet, III, North Carolina M. J. **6**: 61–87, 117–161, 1945.

[3] Allen, F. M., and Sherrill, J. W.: The treatment of arterial hypertension, J. Metabol. Research **2**: 429–545, 1922.

and was hard to administer. General interest in it had virtually disappeared at the time of Kempner's first report.

Kempner [2] based his experiment on the theory that the metabolic (as distinguished from the excretory) function of the kidney cells may be disturbed in renal disease. Such a disturbance might result in the accumulation in the blood and tissues of substances which normally are removed and metabolized by the renal cells or in the appearance of "abnormal" (that is, unusual) substances as a result of disturbed or interrupted metabolic activities of the cells. Such "abnormal" substances might be "harmful" and lead directly or indirectly to hypertension and the anatomical changes associated with it. The various constituents of a mixed diet might furnish a relatively prolific source of such harmful substances. By substituting a rice-fruit-sugar diet the quantity of such harmful substances formed might be decreased and the "renal metabolic dysfunction" thus "compensated." This implies the belief that renal disease (but not necessarily impaired excretory function) is a precursor of essential as well as nephritic hypertension. Neurogenic factors receive little consideration, although Kempner suggests [2] that in those patients with hypertensive vascular disease (not in the terminal stages) who do not respond to the diet, the hypertension must be attributable to extrarenal factors ("neurogenic" or "essential" hypertension). Few will follow Kempner this far, but the point is irrelevant as far as assessing the therapeutic effectiveness of the diet is concerned.

The diet contains 300 gm. of rice (dry weight), 100 gm. (or more) of sugar, 700 to 1000 c.c. of fruit juice with supplementary vitamines and iron. Nothing else, not even water is allowed, in particular no salt, no milk and no fat. This diet furnishes about 2000 calories and contains about 20 gm. protein, 5 gm. fat and 460 gm. carbohydrate, with 0.2 gm. sodium and 0.15 gm. chloride. For patients who require a larger caloric intake, larger quantities are allowed, particularly of sugar and fruit. If there is notable hypochloremia or if symptoms of salt deprivation appear, a small supplement of salt or hydrochloric acid is administered.

With a diet so extremely meager in these electrolytes, it seems inevitable that a serious deficiency should eventually develop. Kempner warns of this danger, insists on frequent examinations of the blood and urine to detect it and cites specific instances of its occurrence. It is impossible, however, from a perusal of his reports to determine how frequently this occurred, how soon it is likely to develop or what supplements are needed to forestall or combat it. The risk is obviously great in patients with impaired renal function.

After from two to five months, in many cases additions are permitted: small amounts of nonleguminous vegetables, potato, lean meat, chicken or fish. Such additions are regarded as reducing substantially the effectiveness of the regime, and they are reduced or eliminated if the improvement which may have occurred on the strict diet is not maintained. In such cases the strict diet should be continued "indefinitely."

This diet is admittedly unpalatable and monotonous. Many patients, particularly at the start, are unable to eat enough to maintain weight so that considerable loss of weight during the first three weeks is common. This may be due also to elimination of edema. According to Kempner, eventually "most patients accustom themselves to the rice diet, and some even like it." Most patients who are kept on the diet apparently reach an equilibrium eventually or even gain weight. One might wish for more detailed information regarding this point than is to be found in his reports. It is clear, however, that the effects of the diet can not be attributed to malnutrition.

It is generally believed that the effectiveness of the diet depends upon its low salt content. There is good experimental evidence that under controlled conditions, significant though moderate fluctuations in blood pressure can be induced by adding or withdrawing salt from the diet. It is probable, also, that it is the sodium rather than the chloride ion which is significant. Although there can be little doubt that rigid reduction in the intake of salt is essential, it has not been proved that this is the only important factor in the Kempner regime.

The diet is manifestly very low in protein, so low that competent investigators doubt the possibility of its maintaining the patient in N equilibrium. Kempner has reported balance studies in patients after two months on the diet in which the urinary N excretion averaged 2.26 gm. in 24 hours. This with an estimated excretion of 0.9 gm. in the feces might be covered by an intake of 20 gm. protein. The accuracy of these figures has been seriously questioned since no one else has been able to maintain human subjects in N equilibrium on vegetable protein only without the excretion of far larger quantities of N in the urine. Schwartz and Merlis [4] studied six individuals on a strict rice diet and found an average daily excretion of N of 5.85 gm. with an intake of 2.63 gm. The negative balance persisted for 90 days in one subject studied for this length of time. Kempner's claim that rice protein has an unusually high biological value is not borne out by analyses which indicate a relative deficiency of several essential amino acids. That the deficiency cannot be excessive in practice is suggested by the fact that, according to Kempner, many patients maintained their weight over long periods and did not show depletion of plasma proteins or develop anemia. To what extent the "strict" diet had been supplemented in these cases Kempner's reports do not show.

Patients on the diet show in the blood a reduction of the non-protein nitrogen and urea nitrogen, of the cholesterol and (moderate) of the chloride. There is an extreme reduction in the excretion of sodium and chloride in the urine, and frequent quantitative estimations of urinary chloride are regarded as essential to determine the degree of coöperation of the patient.

[4] Schwartz, W. B., and Merlis, J. K.: Nitrogen balance studies on the Kempner rice diet, J. Clin. Investigation **26**: 1060–1071, 1947.

Kempner states that relief of subjective discomfort was observed in "a great number" of patients, but only objective evidences of improvement were used in assessing the results of treatment. These were chiefly loss of edema, reversion toward normal of abnormalities in the blood and urine, reduction of at least 20 mm. in mean blood pressure, disappearance of papilledema, retinal hemorrhages and exudates, diminution in width of the cardiac shadow of 18 per cent or more, and reversion to or toward normal of the electrical axis and the inverted T wave in Lead I when these abnormalities were present.

It is impracticable in a brief discussion to analyze Kempner's results in detail. They may be adequately illustrated by his report [5] of 500 cases of hypertensive cardiovascular disease, "most of whom were seriously ill and had failed to respond to other forms of treatment." Two hundred and twenty-nine of these showed evidence of "secondary" renal involvement. Of these 500 cases, 64.4 per cent showed improvement after an average period of treatment of 89 days according to the criteria just mentioned, and 62 per cent showed a significant fall in blood pressure. The length of time required to bring about this reduction in blood pressure varied from four days to 10 months (in one case reported elsewhere [6] it required "almost three years"). The frequency of this response varied with the duration of treatment. Of 195 patients treated less than 35 days, 51 per cent showed a significant fall in pressure, whereas of 305 cases treated from 35 to 898 days, 70 per cent so responded. The average time in which a "marked" decrease in blood pressure was observed was "about three to four months." [6] In 25 per cent of the 500 cases, the pressure fell to normal (less than 145 mm. systolic and 95 mm. diastolic) after an average period of 94 days. Twenty-six patients died while under treatment, and 163 others were not benefited after an average period of 69 days.

The regression of the abnormalities in the fundi, when present, is more impressive. Papilledema, hemorrhages or exudates were present in 140 of the 500 cases, and in 88 photographs were obtained before and after treatment. Papilledema, present in 23 of the 88 cases, disappeared completely in 17 and partly in five. Hemorrhages, present in 55 cases, disappeared completely in 39 and partially in 15. Exudates, present in 70 cases, disappeared completely in 42 and partly in 23. The time required for complete disappearance of these lesions ranged from two to 30 months and averaged 14 months. In several cases improvement occurred without notable reduction in blood pressure.

Objective signs of improvement in the heart were also slow to appear. Of 286 cases studied with reference to the size of the heart, there was a diminution of 10 per cent or more in transverse diameter in 125 (44 per

[5] Kempner, W.: Treatment of hypertensive vascular disease with rice diet, Am. J. Med. **4**: 545–577, 1948.

[6] Kempner, W.: Treatment of heart and kidney disease and of hypertensive and arteriosclerotic vascular disease with the rice diet, Ann. Int. Med. **31**: 821–856, 1949.

cent) after an average period of treatment of 125 days. Of 310 patients with satisfactory tracings, T_1 was diphasic or inverted in 145. In 89 (52 per cent) of these there was a reversion to or toward normal but only after an average period of treatment of 10 months (in one case only after three years).

How long and under what conditions this improvement was maintained and how long the average patient could be held to the regime cannot be clearly determined from Kempner's reports. Specific instances are cited in which patients—presumably on the diet—were well and active four to six years after the treatment was started. Other cases relapsed quickly after the diet was interrupted or prematurely supplemented. One gets the impression that improvement usually persisted as long as the diet was maintained, but that any notable relaxation was often if not usually followed by a fairly prompt relapse. It is also not clear whether or how often the regime had to be abandoned (in effective form) because of electrolyte depletion or other untoward results. Instances are cited in which the diet had to be modified, but Kempner states that no patient has been injured by it.

A skeptical perusal of Kempner's reports reveals a number of aspects which are open to criticism. Although his reports contain a wealth of material including illustrative case reports in detail, there is a great deal of information lacking which one would like to have and which one needs to reach an independent judgment as to the value of the work. Some of these deficiencies have already been referred to.

A more serious one is uncertainty regarding and an apparent lack of an adequate preliminary period of observation. In one of his reports Kempner states (regarding the blood pressure) that "The figures given are averages of the daily readings of three to 24 (average eight) days before and after treatment." A period of more than eight days, preferably at least 30 days, would be required to determine how much of the response in blood pressure is attributable to rest, change in environment and freedom from routine responsibilities, and to suggestion which seems to have been exerted in an unusually effective way, although this may have emanated as much from fellow patients and from the personnel as from the doctors. If this preliminary study had been carried out with as much enthusiasm as was shown in the administration of the diet, there can be little doubt that the basal level of the blood pressure would have been lower in many cases and the additional fall attributable directly to the diet would have been less.

Kempner's critics, however, seem inclined to overstress this defect and to give inadequate regard to other manifestations of improvement. There can be no doubt that these patients had real hypertensive disease. Many who responded well had had serious symptoms for one to several years and had received other types of treatment without relief, including, in at least one case, sympathectomy. The improvement in the fundi, shown in his published photographs, is highly impressive and not lightly to be explained

away by suggestion or inadequate preliminary observation. Furthermore the reduction in blood pressure obtained by suggestion, although often substantial, is rarely long maintained, particularly after the patient returns to his old environment, unless some specific and highly disturbing source of emotional turmoil has been found and eliminated.

Although it is probable that the percentage of patients responding favorably, particularly as judged by the blood pressure, will have to be revised substantially downward, there can be no doubt that many patients showed a marked fall in blood pressure under the regime and an astonishing degree of improvement which can be matched only by some of the patients who have responded favorably to sympathectomy.

If this be conceded, the question naturally arises, why has no adequate confirmation been obtained? There is as yet no satisfactory answer. Several reports have appeared which tend to confirm Kempner's observations. Thus Cantor [7] reported a series of 30 ambulant cases of essential hypertension treated from seven months to a year with a fall to normal in 15 cases and a "decided fall" in nine others. He observed improvement in subjective symptoms, urine, eye grounds and electrocardiograms in most cases. Contratto and Rogers [8] studied 34 coöperative patients with hypertension of at least three years' duration who were kept on the rice diet for at least three months. In 24 there was a definite and persistent drop which in 16 reached 150 mm. systolic and 100 mm. diastolic or less. Subjective symptoms were relieved. Loofbourow et al.[9] administered the diet to 56 ambulant cases of whom 16 adhered well to the diet. Of these, six showed a fall of 20 mm. or more in diastolic pressure, as well as 3 of the 20 "moderate adherers."

On the other hand there have been a number of other studies reported in which the response in blood pressure was negligible or quantitatively so much less than Kempner's that they cannot be regarded as confirmatory. These have been well summarized by Chapman and Gibbons.[10] Some of these were carefully controlled studies on hospitalized patients. Most of them, however, are open to criticism as a direct check of Kempner's work. The number of patients studied was usually small, often only 12 to 20, and the period of treatment relatively short, often four to eight weeks. An adequate check should cover at least as many months. In most of these studies, Kempner's regime was not closely followed, but interest was centered on the effect of restricting the intake of sodium chloride or of sodium. It has not been proved that this is the only important factor in Kempner's regime, and to criticize his work on the basis of experiments which do not essentially duplicate his regime is not warranted at present.

[7] Cantor, H. E.: Ambulatory treatment of hypertension with the rice diet, Pennsylvania M. J. **51**: 1411–1413, 1948.

[8] Contratto, A. W., and Rogers, M. B.: The use of the rice diet in the treatment of hypertension in nonhospitalized patients, New England J. Med. **239**: 531–536, 1948.

[9] Loofbourow, D. G., et al.: The effect of the rice diet on the blood pressure in essential hypertension, New England J. Med. **240**: 910–914, 1949.

[10] Chapman, C. B., and Gibbons, T. B.: The diet and hypertension, Medicine **29**: 29–69, 1950.

Another handicap to securing an adequate check, at least outside a metabolism ward, is the difficulty in securing coöperation of the patients, most of whom find the diet very disagreeable. Even slight deviations from the diet destroy its effectiveness, and the lack of self restraint shown by many human beings in such matters is indeed astonishing. Fear is not an effective deterrent. A form of stimulated enthusiasm seems to be required, approaching religious fervor. Kempner and his group seem to have been highly successful in building up such a faith, and it is here, perhaps, that the powerful factor of suggestion has been most effectively utilized. At any rate, they appear to have secured adequate coöperation from a surprisingly large proportion of their patients, a feat which others find it hard to duplicate.

It is impossible at present to reach any definite conclusion as to the precise value of the Kempner regime. The percentage of patients who are stated to have shown a significant fall in blood pressure is probably too high if the effect of suggestion is to be eliminated. The whole study is somewhat tinged with the enthusiasm of the author, but without this enthusiasm no one could have carried through such a huge piece of work. Unless, however, one arbitrarily dismisses the entire work as totally untrustworthy, there can be no doubt that many severely ill patients have been restored to relatively normal health and the ability to work. How often this may be hoped for is still uncertain.

The results are at least sufficiently promising to warrant a check up in other clinics. To be of value, however, the number of patients should be large, they should be observed for many months, and the work should be unhampered by preconceived ideas as to which features of the diet are most important.

From the practical standpoint, proper administration of the diet is not a simple procedure. It requires fortitude and determination on the part of the patient, close supervision to maintain morale and frequent physical and chemical check-ups to insure adherence to the diet and avoid the danger of hypochloremia. To maintain improvement, the diet, with perhaps modest supplements, will probably have to be maintained indefinitely. As satisfactory results can at best be hoped for in only a fraction of the patients and as there is now no way of selecting those who are likely to respond, the diet hardly seems indicated at present as a routine therapeutic procedure. In patients who are more seriously ill and who do not respond to less troublesome measures, a thorough trial is justified if close supervision is possible and adequate coöperation can be anticipated.

P. W. C.

REVIEWS

Pavlov, A Biography. By B. P. Babkin. 365 pages; 14 × 21.5 cm. The University of Chicago Press, Chicago 37, Ill. 1949. Price, $6.00.

Pavlov is to the physiologist of the brain what Galileo was to the physical scientist, for Pavlov was the first to introduce the experimental method into the physiology of the cerebral function. This he did by his indomitable courage, his skill in the performance of operations, and his ingenuity in devising methods.

At the present time Pavlov is best known for his achievements by the method of the conditional reflex, but when the reviewer was a medical student the conditional reflex did not exist in American medical literature, and Pavlov was then known as a great figure in the physiology of digestion.

To write a biography of Pavlov is under the conditions of our modern world an extremely difficult task even for one who has the ability, insight and diligence to write a biography. Babkin is one of the few men outside of Russia who would be capable of writing a life of Pavlov. In doing this he has executed a most important duty for medical science. It is a duty which can be considered as resting chiefly on Babkin's shoulders, for no one in this country has worked with Pavlov for as long a time or known him over so many years.

The biography is divided into four parts: life; early physiological work; work on digestion; conditional reflexes.

Pavlov's personal life is treated with the fidelity, the loyalty, the objectivity and the unselfishness that is characteristic of Babkin himself. Pavlov's fascinating life story is recounted intimately and unpretentiously without over-dramatization. In order to write this Babkin has drawn not only on his knowledge of Pavlov and Russia but upon the recently published memoirs of his wife, Serafima Pavlova.

Two chapters are devoted to the researches of Pavlov on the blood circulation and the nerves of the heart. Important material is presented on this phase of Pavlov's work. It was here that Pavlov's skill in dealing with the normal intact animal came to light; for Pavlov trained his dogs to lie absolutely quietly while he connected the superficial artery with a manometer. His operation of exposing the artery, which Pavlov with his skill was able to perform in two or three minutes, was apparently painless. By such an experiment he was able to get constant blood pressure at several regular intervals during the month, he recorded an average pressure of 130 mm. with variations not exceeding 20 mm. By such a method Pavlov was able to see that the ingestion of large amounts of fluid had little effect on the blood pressure. His most important work in the cardiac field was published in his doctorate thesis, "The Centrifugal Nerves of the Heart." Here he investigated the effect of the vagus on the rhythm and strength of contraction. He classified the cardiac nerves into four kinds—now known to be only the sympathetic and parasympathetic. This work of Pavlov was done at the same time as that of Gaskell in England, and as the latter work was published in English, Pavlov's has attracted little attention.

Next followed Pavlov's great contributions to the physiology of digestion, for which he received the Nobel Prize in 1903. It was in this branch of physiology that Pavlov showed his brilliance by the ability to devise methods of working with the normal and intact animal over a long period. This he did chiefly through the introduction of the method of the chronic fistula. He obtained and measured under normal living conditions the secretion of the stomach and the gall bladder. Due to Pavlov's surgical skill and physiological insight he was the first to obtain a true secretion of the isolated stomach; Heidenhain, the great Breslau physiologist, had failed because he severed the gastric branches of the vagus nerve coursing within

the walls of the stomach. These Pavlov preserved by incising only through the mucosa. With the present interest in sympathectomy for pancreatitis it is timely to note that Pavlov was the first to demonstrate nerves both stimulating and suppressing the pancreatic secretion.

The section on the conditional reflexes gives an interesting historical background, but many of the facts of Pavlov's discoveries in this field have been omitted. This is not especially serious, since the material on the last 35 years of Pavlov's work is available in three books which have been translated into English (two of them by the present reviewer and one of them by another pupil of Pavlov's, Anrep).

This book is a valuable addition to the library of those physicians interested in medical history and biography as well as to those who have a special stake in the fields in which Pavlov worked.

W. Horsley Gantt

Electrocardiography—Fundamentals and Clinical Application. By Louis Wolff, M.D., Visiting Physician, Consultant in Cardiology and Chief of the Electrocardiographic Laboratory, Beth Israel Hospital. 187 pages; 16.5 × 25 cm. W. B. Saunders Company, Philadelphia. 1950. Price, $4.50.

This excellent treatise on electrocardiography is divided into two parts. The first deals with the electrical phenomena which accompany myocardial contraction and which are of practical value in interpreting the clinical electrocardiogram. Part II applies these basic principles to the analysis of tracings commonly seen in practice. Arrhythmias are not discussed, since their interpretation does not depend on a comprehension of the underlying electrical phenomena. Those conditions which are covered in detail are bundle branch block, ventricular hypertrophy, coronary artery disease and myocardial infarction, pericarditis, pulmonary embolism and the Wolff-Parkinson-White syndrome.

The casual observer may be forgiven for asking if yet another text on electrocardiography is really necessary. To the careful reader, however, this book will reveal itself to be unique and valuable.

Dr. Wolff, from his many years of teaching electrocardiography at Harvard, found that the conventional method of empirical interpretation had disadvantages. So he changed his tactics to presenting basic principles first, without referring to patterns. His book is written with the same approach, and the reader will have no difficulty in believing the author's claim that his students, under his revised system of teaching, "were able to predict the character of the precordial and extremity curves in the normal heart and in various pathologic conditions before actually studying electrocardiograms, they acquired skill and exercised restraint in interpreting records, and they were able to retain their knowledge."

The text is clearly and simply written, and is amply illustrated. The author is not, however, sufficiently explicit in his definition of intrinsicoid deflections to make them always easy of recognition and accurate timing in subsequent tracings. For example, from the description available, it is impossible to appreciate the significant changes which are claimed to have occurred in the timing of the intrinsicoid deflections of figures 86 and 87. This lack of clear definition and description of the technic of timing them is a pity, because of the great importance of these deflections.

To the reviewer, who has been instructed and instructing along inferior empirical lines, the logical and revealing approach which is here employed, has made exciting reading. This text can be strongly recommended to student, general practitioner, and many an internist and cardiologist.

H. J. L. M.

Unipolar Lead Electrocardiography. 2nd Ed. By EMANUEL GOLDBERGER, B.S., M.D., Adjunct Physician, Montefiore Hospital, N. Y.; Lincoln Hospital, N. Y.; St. Joseph's Hospital, Yonkers, N. Y.; Lecturer in Medicine, Columbia University. 392 pages; 15.5 × 24 cm. Lea & Febiger, Philadelphia. 1949. Price, $7.50.

Electrocardiography as now taught almost everywhere emphasizes unipolar leads, following the work of Wilson and his associates in 1934, though Wilson's place as the pioneer in this field is difficult to discover by reading this text. This second edition of Goldberger's text is larger than the first, and many of the errors of the first edition have been corrected. The volume is not complete enough in its contents nor exact enough in its statements to serve as an independent text on electrocardiography. As a brief opus, it is not as lucid as some of the recently published books on electrocardiography, which are also concerned primarily with unipolar leads, although not so titled.

S. S.

Obesity. By EDWARD H. RYNEARSON, M.D., F.A.C.P., Division of Medicine, Mayo Clinic, Associate Professor of Medicine, Mayo Foundation; and CLIFFORD F. GASTINEAU, M.D., Fellow in Medicine, Mayo Foundation. 134 pages; 22.5 × 14.5 cm. Charles C. Thomas, Springfield, Ill. 1949. Price, $3.50.

This short book reads so swiftly that the many facts concentrated in nearly every sentence can easily be missed. Striding deftly on and over past concepts and conceits of the overweight problem, the authors make a good case for the thesis that obesity is "simply the result of a large appetite and decreased activity." The physiology of obesity is simplified to a calorie-surface area equilibrium. Associated phenomena are explained as the results—not the causes—of the obesity, the establishment of new habits of eating the only "cure."

The case for non-obesity is succinctly shown, contraindications to weight reduction are briefly and summarily disposed of, and dietary management is smoothly presented, with a brief exploring of psychotherapy and cataloguing of other methods of treatment. The bibliography has 422 items.

If obese patients could be persuaded to read and digest this excellent book, the lot of their guiding physicians would be so much easier.

C. B. A.

You and Your Fears. By PETER J. STEINCROHN, M.D., F.A.C.P., introduction by C. Charles Burlingame, M.D., F.A.C.P. 224 pages; 13.5 × 20 cm. Doubleday & Co., Inc., Garden City, N. Y. 1949. Price, $2.50.

Dr. Steincrohn, who says that he writes as an internist and not as a psychiatrist, talks about the patients that come daily to the office of a physician. He calls them the "unduly anxious individuals." The author is convinced that they are not getting enough help. He attempts to give the reader (whom he considers more or less neurotic, like all human beings) a "new frame for the old picture." He does not pretend to cure the neurotics but he promises "some hope for the hopeless" by showing him how he might live and be happy. He does this in 29 brief chapters. He admits that there are not enough trained psychiatrists to treat the neurotics of today but he feels that any "unhurried" physician who can listen sympathetically is able to help you and your fears.

H. W. N.

BOOKS RECEIVED

Books received during March are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

The Common Infectious Diseases: A Handbook for Students and Postgraduates. By H. STANLEY BANKS, M.A., M.D. (Glas.), F.R.C.P. (Lond.), D.P.H. (Cantab.), Physician-Superintendent, Park Hospital, Hither Green, London, etc. 354 pages; 22 × 14 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, $4.50.

Compulsory Medical Care and the Welfare State: An analysis based on a special study of Governmentalized Medical Care Systems on the Continent of Europe and in England. By MELCHIOR PALYI. 156 pages; 23 × 15 cm. (paper-bound). 1950. National Institute of Professional Services, Inc., Chicago. Price, $2.00.

Current Therapy, 1950: Latest Approved Methods of Treatment for the Practicing Physician. Editor: HOWARD F. CONN, M.D.; Consulting Editors: M. EDWARD DAVIS, VINCENT J. DERBES, GARFIELD G. DUNCAN, HUGH J. JEWETT, WILLIAM J. KERR, PERRIN H. LONG, H. HOUSTON MERRITT, PAUL A. O'LEARY, WALTER L. PALMER, HOBART A. REIMANN, CYRUS C. STURGIS, and ROBERT H. WILLIAMS. 736 pages; 28 × 20.5 cm. 1950. W. B. Saunders Company, Philadelphia. Price, $10.00.

The Cytologic Diagnosis of Cancer. By THE STAFF OF THE VINCENT MEMORIAL LABORATORY OF THE VINCENT MEMORIAL HOSPITAL, A Gynecologic Service Affiliated with the Massachusetts General Hospital, Boston, Massachusetts; The Department of Gynecology, Harvard Medical School; Published under the Sponsorship of The American Cancer Society. 229 pages; 25.5 × 16.5 cm. 1950. W. B. Saunders Company, Philadelphia. Price, $6.50.

Danger! Curves Ahead! How to Prevent and Correct Overweight. By MIRIAM LINCOLN, M.D., F.A.C.P., Clinical Assistant, Professor of Medicine, School of Medicine, University of Washington. 138 pages; 21 × 14 cm. 1948. The Macmillan Company, New York. Price, $2.50.

Medical Management of Gastrointestinal Disorders. By GARNETT CHENEY, M.D., Clinical Professor of Medicine, Stanford University Medical School. 478 pages; 21 × 14.5 cm. 1950. The Year Book Publishers, Inc., Chicago. Price, $6.75.

Penicillin: Its Practical Application. 2nd Ed. Under the General Editorship of PROFESSOR SIR ALEXANDER FLEMING, M.B., B.S., F.R.C.P., F.R.C.S., F.R.S., Professor Emeritus of Bacteriology, University of London, etc. 491 pages; 22 × 14 cm. 1950. The C. V. Mosby Company, Saint Louis. Price, $7.00.

A Primer of Venous Pressure. By GEORGE E. BURCH, M.D., Henderson Professor of Medicine, Tulane University School of Medicine, etc. 174 pages; 24 × 15.5 cm. 1950. Lea & Febiger, Philadelphia. Price, $4.00.

Proceedings of the First Clinical ACTH Conference. By JOHN R. MOTE, M.D., Editor. 607 pages; 23.5 × 15.5 cm. 1950. The Blakiston Company, Philadelphia. Price, $5.50.

Progress in Clinical Endocrinology. Edited by SAMUEL SOSKIN, M.D., Director, Medical Research Institute, Michael Reese Hospital, Chicago, Illinois, etc. 641 pages; 23.5 × 15.5 cm. 1950. Grune & Stratton, New York. Price, $10.00.

Research in Medical Science. Edited by DAVID E. GREEN, Ph.D., and W. EUGENE KNOX, M.D. 492 pages; 24. × 15.5 cm. 1950. The Macmillan Company, New York. Price, $6.50.

Surgical Treatment for Abnormalities of the Heart and Great Vessels (The Beaumont Lecture, Wayne County Medical Society, Detroit, Michigan). 1st Ed., 2nd printing. By ROBERT E. GROSS, M.D., William E. Ladd Professor of Child Surgery, Harvard University Medical School. 72 pages; 22 × 14.5 cm. (limp leather binding). 1950. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $2.00.

Thrombosis in Arteriosclerosis of the Lower Extremities. By EDWARD A. EDWARDS, M.D., F.A.C.S., Diplomate of American Board of Surgery, Clinical Associate in Anatomy, Harvard Medical School, etc. 74 pages; 22 × 14.5 cm. (limp leather binding). 1950. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $2.00.

The Tuberculous Process: A Conception and a Therapy. A Private Study. By ALFRED LEITCH, M.B., Ch.B. (Edin.), Formerly Tuberculosis Officer, Royal Chest Hospital. 175 pages; 19 × 12.5 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, $3.00.

COLLEGE NEWS NOTES

Postgraduate Courses

The following A.C.P. Postgraduate Courses are still open for registration:

Course No. 8, INTERNAL MEDICINE, University of California Medical School, San Francisco, Calif., June 19–23, 1950, Stacy R. Mettier, M.D., F.A.C.P., Director. Fees: A.C.P. Members, $30.00; Non-members, $60.00.

Course No. 9, CLINICAL ASPECTS OF MALNUTRITION, Hospital de Enfermedades de la Nutrición, Mexico, D. F., August 16–25, 1950, Salvador Zubirán, M.D., F.A.C.P., Director. Fees: A.C.P. Members, $60.00; Non-members, $120.00.

Address inquiries to the Executive Secretary, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

Announcement of the Autumn Courses for 1950 will be made in the June issue of this journal.

A.C.P. Regional Meetings

Dates for several of the Regional Meetings for the Autumn of 1950 have been selected and the following are announced:

Oklahoma-Arkansas Regional Meeting, Tulsa, Okla., September 30, 1950.
Western New York Regional Meeting, Rochester, N. Y., October 14, 1950.
New Jersey Regional Meeting, Trenton, N. J., November 1, 1950.
Northwest Regional Meeting, Portland, Ore., November 10–11, 1950.
Utah Regional Meeting, Salt Lake City, Utah, November 11, 1950.
Colorado Regional Meeting, Denver, Colo., November 11, 1950.
Midwest Regional Meeting (Illinois, Indiana, Iowa, Michigan, Minnesota, Ohio and Wisconsin), Madison, Wis., November 18, 1950.
Kentucky Regional Meeting, Lexington, Ky., December 9, 1950.

Numerous other regional meetings are in course of preparation and announcement will be made later.

New Life Members

The College is gratified to announce that the following Fellows, in order listed, have become Life Members of the American College of Physicians since the publication of the latest issue of this journal:

Nathan Smith Davis, III, Chicago, Ill.
Isidore Isaac Hirschman, Huntington, W. Va.
Kyran E. Hynes, Seattle, Wash.
Artell Egbert Johnson, New York, N. Y.
Daniel Michael McCarthy, Brooklyn, N. Y.
Joseph Bedford Vander Veer, Philadelphia, Pa.
Robert Theodore Lucas, Shreveport, La.
Samuel E. Cohen, Elmira, N. Y.
C. Howard Marcy, Pittsburgh, Pa.
James Risley Reuling, Bayside, N. Y.
James Rubeo Lisa, New York, N. Y.
Andrew J. V. Klein, East Orange, N. J.

The College has an equitable and practicable Life Membership plan whereby members may underwrite their future dues during their productive years, while income is greatest. Life Membership offers security in advancing years against misfortunes which often necessitate the relinquishment of one's most cherished professional memberships because of the burden of dues. All Life Membership fees are added to the permanent Endowment Fund of the College, and thus contribute to the security of the College as well as to the security of its members. The Life Membership fee is deductible on Federal income tax returns, thus offering very substantial savings to the subscriber.

The Board of Trustees of the America Medical Association met on February 9, 10 and 11, and has announced the following appointments:

Dr. Walter B. Martin, F.A.C.P., Norfolk, Va., appointed a member of the Executive Committee.

Dr. F. F. Borzell, F.A.C.P., Philadelphia, Pa., appointed to the Fifty-Fourth Annual Meeting of the American Academy of Political and Social Sciences.

Dr. L. H. Bauer, F.A.C.P., Hempstead, N. Y., appointed to the American Council on Rheumatic Fever.

Dr. T. P. Murdock, F.A.C.P., Meriden, Conn., appointed to the National Committee for the Improvement of Nursing Services.

Dr. Joseph M. Hayman, F.A.C.P., Cleveland, Ohio, appointed to the Council on Pharmacy and Chemistry.

The Spencer Road Sanitarium, Oklahoma City, Okla., was presented as an outright gift to the Oklahoma Medical Research Foundation late in February by Dr. Coyne H. Campbell, F.A.C.P., who founded the hospital. The Sanitarium is valued at $250,000, can accommodate 90 patients, and is designed for chronic and convalescent psychopathic patients and alcoholics. It includes nearly eight acres of land, a hospital building, three cottages, a dining hall, kitchen, treatment rooms, and a storage building.

Psychiatric Residency Program

The Psychiatric Training Faculty of Massachusetts is receiving applications for residency training in basic psychiatry at first, second, and third year levels, to begin July 1, 1950.

Three psychiatric hospitals, Boston State Hospital, Boston Psychopathic Hospital, and Worcester State Hospital, and the psychiatric facilities of the Judge Baker Guidance Center, Massachusetts General Hospital, and Massachusetts Memorial Hospital, are engaged in an integrated program giving training in basic psychiatry and neurology.

The program provides a rotating residency to afford the resident training in inpatient work with psychotic, psychosomatic, and psychoneurotic patients, out-patient work with children and adults, affiliation with university teaching programs, grounding in basic neurology and psychology, and supervision in a wide range of psychiatric therapies. Opportunities are also afforded for psychoanalytic training for a limited number of candidates under the auspices of the Boston Psychoanalytic Institute. Arrangement for such training is dependent on acceptance by the Institute.

For some of these residencies, stipends are made available by the U. S. Public Health Service from grants provided through the National Mental Health Institute.

The stipend at the first-year level is $2,000 per year, at the second-year level $2,400, and at the third-year level $3,000.

For further information write to:

Henry A. Tadgell, M.D., F.A.C.P., Secretary
PSYCHIATRIC TRAINING FACULTY OF MASSACHUSETTS
15 Ashburton Place, Room 802
Boston, Mass.

The National Paraplegia Foundation wishes to announce the establishment of a limited number of fellowships for research in spinal cord disease and trauma and in the complications commonly associated with such disease or injury. These fellowships carry a minimum stipend of $3,000 per year and may be awarded to any candidate who has demonstrated a capacity for medical research and has outlined a program of meritorious study. The fellowships will be awarded by the Medical Advisory Committee and are open for award for the academic year 1950–1951. Application forms may be obtained from the Chairman of the Medical Advisory Committee, and applications should be submitted to him not later than June 1, 1950.

L. W. Freeman, M.D.
Chairman, Medical Advisory Committee
National Paraplegia Foundation

POSTGRADUATE COURSE IN PSYCHIATRY AND NEUROLOGY

The University of California School of Medicine announces a twelve week postgraduate course in Psychiatry and Neurology to be given by the Division of Psychiatry, in coöperation with University Extension (Medical Extension), University of California, from August 28 through November 17, 1950. The course is open only to qualified physicians. Instruction will be under the direction of Dr. Karl M. Bowman, Professor of Psychiatry, University of California School of Medicine. The subjects covered will include:

> General Psychiatry, Child Psychiatry, Psychobiology, Psychoanalysis, Psychology and Psychopathology, Functional and Organic Psychoses, Psychoneuroses, Therapy, Psychosomatic Problems, Neuroanatomy, Clinical Neurology, Neuropathology, Neurophysiology, Electroencephalography, X-Ray Diagnosis, Cultural Anthropology, and other related topics.

The course is particularly designed to prepare psychiatrists and neurologists for examinations of the American Board of Psychiatry and Neurology, and is therefore designed for the advanced student in Psychiatry and Neurology. The fee for the course is $200.00. For application and full details address:

Stacy R. Mettier, M.D., Professor of Medicine
Head of Postgraduate Instruction, Medical Extension
University of California Medical Center
San Francisco 22, California.

The annual D. J. Davis Lecture on Medical History at the University of Illinois College of Medicine was delivered by Dr. Joseph A. Capps, F.A.C.P., Emeritus Professor of Clinical Medicine, University of Chicago School of Medicine, on March 29.

At the twenty-fifth anniversary observance of the opening of the University of Illinois Research and Educational Hospitals on April 1, Dr. Carroll L. Birch,

F.A.C.P., Dr. Edmund F. Foley, F.A.C.P., and Dr. Francis E. Senear, F.A.C.P., were among those presented with keys in recognition of twenty-five years continuous service. Dr. Andrew C. Ivy, F.A.C.P., Vice President of the University in charge of the Chicago Professional Colleges, made the presentations.

Dr. J. C. Geiger, F.A.C.P., Director of Public Health, San Francisco, was honored on March 15 by the Minister of Public Health and the Military Junta of Venezuela, who conferred on him the Order of El Libertador in the grade of Commander. Dr. Geiger's citation stated that this honor was "For distinguished services to Venezuela and its citizens, particularly in the field of child and maternal welfare, and public health administration."

The Colorado Rheumatic Fever Library has been established at the University of Colorado School of Medicine in response to the great need for the assembling in one place of all that has been written on the subject of rheumatic fever. It is desired that this library contain reprints or copies of every article that has been written on rheumatic fever. This material will be cross-indexed and assembled in bound volumes by years, and will ultimately be made available to all workers in the field of rheumatic fever in the form of a photostat and an abstract service. Valuable assistance can be given by all those writing in the field of rheumatic fever, and all those willing to dispose of reprint collections, by contributing papers relating to rheumatic fever. Reprints and inquiries should be sent to:

Ward Darley, M.D., Dean
University of Colorado School of Medicine
and Hospitals
4200 East Ninth Avenue
Denver 7, Colorado.

The Connecticut State Medical Society held its annual meeting in Waterbury, May 2–4, under the Presidency of Dr. Charles H. Sprague, F.A.C.P., Bridgeport. Among the speakers were Dr. Mandred W. Comfort, F.A.C.P., Rochester, Minn.; Dr. Edward J. Stieglitz, F.A.C.P., Washington, D. C., and Dr. Tom D. Spies, F.A.C.P., Birmingham, Ala. Dr. Thomas P. Murdock, F.A.C.P., Meriden, presided at a symposium on anemias, blood dyscrasias and blood therapy, and Dr. C. Charles Burlingame, F.A.C.P., Hartford, presided at the symposium on endocrine subjects.

The American Trudeau Society, in coöperation with the University of Pittsburgh School of Medicine and Graduate School of Public Health and the Industrial Hygiene Foundation of America, conducted a postgraduate course in "Pulmonary Diseases and Their Relation to Employment" at the University of Pittsburgh, May 15–19, 1950. Dr. C. Howard Marcy, F.A.C.P., Pittsburgh, is Chairman of the Regional Subcommittee of the American Trudeau Society, having to do with medical education for this section of the country.

Dr. Paul D. Camp, F.A.C.P., of Richmond, has been appointed Assistant Professor of Clinical Medicine at the Medical College of Virginia.

Dr. Leon L. Gardner, F.A.C.P., has been appointed Chief of Preventive Medical Service in the Richmond (Virginia) City Health Department.

The American Association of Pathologists and Bacteriologists held its annual meeting at the University of Wisconsin Medical School, Madison, April 13–15, under the Presidency of Dr. Shields Warren, F.A.C.P., Boston, Mass.

In appreciation of 25 years of service a testimonial dinner was given to Dr. Abraham M. Rabiner, F.A.C.P., on March 12, by the medical staff of the Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn, N. Y., where Dr. Rabiner is Director of Neurology and Clinical Director. At the same time it was announced that the board of directors of the institution has established the Dr. Abraham M. Rabiner Research Fellowship.

The first issue of the *Journal of the Philadelphia General Hospital* has just been published. It is a quarterly published by the hospital, and is edited by Dr. Pascal F. Lucchesi, F.A.C.P., Superintendent and Medical Director. The Consulting Board of Editors includes Dr. William P. Boger, F.A.C.P., Dr. Jefferson H. Clark, F.A.C.P., and Dr. Thomas M. McMillan, F.A.C.P., all of Philadelphia.

Dr. Charles L. Dunham (Associate), Washington, D. C., has been appointed Chief of the Medical Branch, Division of Biology and Medicine, of the Atomic Energy Commission. Dr. John Z. Bowers (Associate) has been made special assistant to Dr. Shields Warren, Director, Division of Biology and Medicine.

Dr. Albert M. Snell, F.A.C.P., has retired from the Mayo Clinic, Rochester, Minn., and is now associated with the Palo Alto Clinic at Palo Alto, Calif.

Dr. William N. Chambers (Associate), Cincinnati, Ohio, was among the speakers at the annual meeting of the American Psychosomatic Society, held in Atlantic City on April 29. Dr. Eugene B. Ferris, F.A.C.P., is President of the Society, and Dr. Sydney G. Margolin (Associate), is Secretary-Treasurer.

Dr. Robert G. Bloch, F.A.C.P., Professor of Medicine, University of Chicago School of Medicine, delivered the annual John W. Bell Tuberculosis Lecture of the Hennepin County Medical Society and the County Tuberculosis Association on April 3. His subject was "Relationship of Sarcoidosis to Tuberculosis."

Dr. N. C. Gilbert, F.A.C.P., Chicago, retired as Chief Editor of the *Archives of Internal Medicine* on January 1, 1950. He was head of the Editorial Board from 1932 to 1937 and had been the Chief Editor since that time. He is succeeded by Dr. Paul S. Rhoads, F.A.C.P., Chicago.

1949 AUDITOR'S REPORT AND STATEMENT OF OPERATIONS THE AMERICAN COLLEGE OF PHYSICIANS

February 12, 1950

To the BOARD OF REGENTS
AMERICAN COLLEGE OF PHYSICIANS, INC.
4200 Pine Street
Philadelphia 4, Pa.

Dear Sirs:

I have examined the accounts of the

AMERICAN COLLEGE OF PHYSICIANS, INC.

for the year ended December 31, 1949, and the accompanying statements, including the BALANCE SHEET at December 31, 1949, the analyses of the GENERAL FUND and the ENDOWMENT FUND and the STATEMENT of the INCOME ACCOUNT FOR THE CALENDAR YEAR 1949, are in accordance with the books of Account, and in my opinion present

fairly the financial position at December 31, 1949, and the results of operations for the calendar year 1949, in conformity with generally accepted accounting principles applied on a basis consistent with that of the preceding years, and subject to the following comments:

Cash: The cash was properly accounted for, was confirmed by direct correspondence with the following depositories, and the Petty Cash verified:

Girard Trust Company, Philadelphia	$ 82,553.03
Provident Trust Company, Philadelphia	15,238.61
Royal Bank of Canada, Montreal	2,612.53
Petty Cash	250.00
	$100,654.17

Accounts Receivable: The Accounts Receivable were examined and found to be less than one year old and appear to be collectible. The detailed accounts receivable were in agreement with the control account. No requests for confirmation of the accounts were mailed.

Investments: The securities were accounted for by direct correspondence and the income for the period under review was verified. The investment transactions are recorded properly in the general books of account and in the Investment Ledger, which is in agreement with the investment accounts of the General Ledger.

General: The changes in the amount of the ENDOWMENT FUND and the GENERAL FUND during the year 1949 are as follows:

Fund	*Balance Jan. 1, 1949*	*Balance Dec. 31, 1949*	*Increase*
General Fund	$299,616.61	$339,668.68	$40,052.07
Endowment Fund	285,340.62	307,199.64	21,859.02
James D. Bruce Fund	10,395.83	10,395.83	
A. Blaine Brower Fund	5,031.25	7,656.25	2,625.00
	$600,384.31	$664,920.40	$64,536.09

The Executive Secretary has analyzed the income of the ANNALS according to Volume, so that the income and expenses are stated according to the year of publication, with the exception of Volumes of prior years, which are closed out and not carried in an inventory account, with the sales properly credited to the General Fund according to the date of sale.

General Comments: The prepaid insurance at December 31, 1949, was not set up as a deferred expense; the other deferred and accrued items were verified; the charges to the Furniture and Equipment Accounts represent proper additions to this account, and the allowances for depreciation appear to be adequate. A depreciation reserve account has been set up for the Headquarters Building in accordance with the action of the Board of Regents at the meeting on December 12, 1937, which provided that depreciation on the Building should be taken into account at the rate of $1,000.00 per year, and increased in 1949 to $2,000.00, due to the addition to the building. The footings and extensions of the inventory were verified.

All ascertainable liabilities have been included in the Balance Sheet.

All recorded receipts from dues, initiation fees, exhibits, advertising, sales of publications, etc., were properly deposited in bank, and all disbursements, as indicated by the vouchers, cancelled checks and bank statements were properly recorded in the books of account.

Respectfully submitted,

DAVID ROBINOVITZ, *Auditor*

Balance Sheet, December 31, 1949

General Fund

Assets		
Current:		
Cash in Banks and on Hand		$ 97,210.44
Accounts Receivable		6,320.66
American Air Lines		425.00
Inventory of Keys, Pledges and Frames, at cost		1,077.17
Accrued Income on Endowment Fund Investments		1,506.44
Accrued Income on General Fund Investments		619.37
Investments at Book Value		191,572.70
Insurance Deposit		555.00
Total Current Assets		299,286.78
Deferred:		
Expenses, 31st Annual Session	3,993.70	
Advertising, Volume XXXII	9.85	
1949 Directory	2,024.06	6,027.61
Fixed		
College Headquarters:		
Real Estate	112,882.32	
Less Depreciation	14,000.00	98,882.32
Furniture and Equipment, at cost	19,935.70	
Less Depreciation	12,794.59	7,141.11
Investment, Real Estate, 404-12 S. 42nd St.		9,647.72
		$420,985.54

Liabilities	
Current:	
Accounts Payable	$ 259.05
Philadelphia Income Tax	38.25
Deferred Income:	
Advance Subscriptions, Annals of Internal Medicine, Volumes XXXII to XXXXII	54,678.76
1950 Exhibits	14,072.06
Restricted Funds:	
Income on James D. Bruce Fund Investments	395.83
Income on A. Blaine Brower Fund Investments	156.25
Reserve, 1949-50 Research Fellowship Fund	9,416.66
Reserve, 1950-51 Research Fellowship Fund	2,300.00
Total Current Liabilities and Funds	$ 81,316.86
General Fund, as annexed	339,668.68
	$420,985.54

Endowment Fund

Assets	
Current:	
Cash	$ 943.73
Investments at Book Value	306,255.91
Accrued Income on Investments	1,506.44
	$308,706.08

Liabilities	
Current:	
Endowment Fund, Principal	$307,199.64
Accrued Income, Due to General Fund	1,506.44
	$308,706.08

James D. Bruce Fund

Current:	
Investments in U. S. Government Bonds	$ 10,000.00
Cash	395.83
	$ 10,395.83

Current:	
Principal	$ 10,000.00
Accumulated Income	395.83
	$ 10,395.83

A. Blaine Brower Fund

Current:	
Cash	$ 2,656.25
Investments in U. S. Government Bonds	5,000.00
	$ 7,656.25

Current:	
Principal	$ 7,500.00
Accumulated Income	156.25
	$ 7,656.25

(Total Assets, $747,743.70)

(Total Liabilities and Funds, 747,743.70)

Summary of Operations for the Calendar Year 1949

Income:			
Annual Dues		$42,934.00	
Initiation Fees		19,736.00	
Subscriptions, Annals of Internal Medicine		99,502.77	
Advertising, Annals of Internal Medicine		23,148.26	
Income from Investments, General Fund (including Accrued)		10,151.16	
Income from Investments, Endowment Fund (including Accrued)		11,716.12	
Dividend on Perpetual Insurance Deposit		60.00	
Sale of 1948 Membership Roster		18.62	
Midwest A. C. P. Regional Meeting		639.32	
Postgraduate Courses, Balance		2,544.10	
Miscellaneous Income (Dr. W. G. Leaman's gift)		375.00	
Rent—404-12 S. 42nd Street (net)		354.02	
Profit on Sale or Maturity of Securities, General Fund		195.75	
Profit on Equipment Traded in		37.50	
Thirtieth Annual Session:			
Exhibits	$22,548.24		
Guest Fees	2,688.54	25,236.78	
Total Income			$236,649.40
Expenses:			
Salaries		$51,353.02	
Communications (Postage, Telephone, Telegraph)		7,800.24	
Office Supplies and Stationery		2,762.24	
Printing		66,085.60	
Traveling Expenses		8,218.75	
Rent and Maintenance (including Annual Session)		6,085.26	
College Headquarters—Maintenance, Taxes, Insurance, etc.		5,248.66	
Gift, Conference Committee on Graduate Training in Med.		2,500.00	
Depreciation on College Headquarters Building		2,000.00	
Depreciation on Furniture and Equipment		1,033.76	
Keys, Pledges and Frames		114.88	
John Phillips Memorial Prize		69.75	
Investment Counsel Service and Security Custodian's Fee		808.00	
Employees' Pension Fund		6,605.25	
Collection and Exchange		19.26	
Regional Meetings		3,253.56	
Loss on Sale of Securities, General Fund		813.33	
General Miscellaneous		2,278.49	
Thirtieth Annual Session—Special Expenses:			
Banquet Deficit	$ 478.93		
Committee on Panels	102.73		
Committee on Publicity	931.28		
Committee on Ladies' Entertainment	764.63		
Committee on Clinics	50.00		
Convocation	1,233.20		
Governors-Regents Expenses	1,104.82		
Grand Reception Deficit	28.32		
Radio City Music Hall Deficit	85.90		
Registration	346.90		
Other Miscellaneous	2,337.35	7,464.06	
Total Expenses			$174,514.11
Net Income for 1949 Credited to General Fund			$ 62,135.29

OBITUARIES

DR. JAMES RAE ARNEILL, SR.

Dr. James Rae Arneill, Sr., F.A.C.P., died January 27, 1950, and in his passing the Rocky Mountain Area lost one of its most outstanding physicians, the University of Colorado School of Medicine, one of its honored teachers and the American College of Physicians, a member who has played a very important part in its history.

Dr. Arneill was born in De Pere, Wisconsin, in 1869. He took his A.B. degree in 1890 from Lawrence University, Wisconsin, and in 1894 his M.D. degree from the University of Michigan School of Medicine. Following his graduation in medicine Dr. Arneill pursued postgraduate studies in Vienna and at Harvard and served on the faculty of the University of Michigan School of Medicine.

In 1903 he moved to Denver and from that date until his death conducted a very active practice in Internal Medicine, and at the time of his death was the central figure in one of the large clinics of the Rocky Mountain Area and was active on the staffs of all the Denver hospitals, particularly the staff of St. Lukes. In recognition of his services to this hospital, its Board of Managers has established the James Rae Arneill Memorial Library.

In 1916 Dr. Arneill retired from active teaching on the faculty of the University of Colorado as an Emeritus Professor of Medicine. His teaching activities for the University played a very important part in the early development of its School of Medicine. In 1905 he published a textbook, *Clinical Diagnosis and Urinalysis*, which, in its day, contributed much to medical teaching throughout the nation.

Dr. Arneill was elected to Fellowship in the American College of Physicians in 1917, just two years after its founding. He was a most important figure in the early development of the College, serving as Regent in 1922–23 and again from 1927 to 1933. He also served as College Governor of Colorado between 1922 and 1926 and following this he was Associate Editor of *The Annals of Internal Medicine* for a number of years. Dr. Arneill became a life member of the College in 1936. He was a Diplomate of the American Board of Internal Medicine, a Fellow of the American Medical Association and its component organizations and of many other professional organizations.

In addition to his activities in the field of community service, medical education and the activities of the College, Dr. Arneill will be remembered as a genial, kindly, conscientious physician who exemplified the fine spirit of American Medicine in the highest possible manner.

WARD DARLEY, M.D., F.A.C.P.
Governor for Colorado

DR. LEE CONNEL GATEWOOD

Quietly in the early morning of January 3, 1950, after a series of myocardial infarctions extending over seven years, death came to Lee Connel Gatewood. This peaceful departure seemed peculiarly fitting for a man whose life had been an exemplification of humility, serenity, modesty, and friendly charm. It was also in the tradition of the Gatewood family for his two brothers, Dr. Gatewood Gatewood and Dr. Wesley Gatewood, had preceded him in death from coronary disease as had his father, Dr. Wesley Emmet Gatewood, and all of his father's six brothers.

Dr. Lee Gatewood was born in Stockport, Ohio, March 15, 1889; he graduated from Ohio State University and Rush Medical College; he furthered his medical education at the University of Vienna. Upon returning to Chicago he became an associate of Bertram W. Sippy. In World War I, Dr. Gatewood served with Base Hospital 13 and was discharged with the rank of Major. After the war he returned to the staff of the Presbyterian Hospital of Chicago. He continued to teach until his death, for many years as Clinical Professor of Medicine of Rush Medical College, later as Professor of Medicine of the University of Illinois. He served as attending physician to the Presbyterian and Highland Park Hospitals. For twenty years he was a faithful member of the staff of the Cook County Hospital. As a consultant he visited various other hospitals including the Hines General Hospital. At the time of his death he was President of the Board of Trustees of Rush Medical College. He was a member of various medical societies including the Chicago Society of Internal Medicine (one-time President), the Chicago Institute of Medicine, the Chicago Pathologic Society, the Central Society for Clinical Research, the American Medical Association, and the American Gastroenterological Association. He was a diplomate of the American Board of Internal Medicine and certified in Gastroenterology. He became a Fellow of the American College of Physicians in 1937.

Dr. Gatewood is survived by Grace Blair Gatewood, whom he married in 1914; by their two children, Lee C. Gatewood, Jr., and Mrs. Walter Senters of Columbus, Ohio; by his mother, Mrs. Wesley Emmet Gatewood of Columbus, Ohio; and by a host of devoted friends and loyal patients. His life was one of service generously given, of tasks cheerfully assumed and faithfully discharged; of courageous living in spite of the knowledge that death would probably strike soon and suddenly. The world is better because of him. We mourn the loss of a dear friend, yet we cherish his memory and the inspiration of his life.

Walter L. Palmer, M.D., F.A.C.P.,
Governor for Northern Illinois

DR. HAROLD EDSON WRIGHT

On January 16, 1950, Dr. Harold Edson Wright, F.A.C.P., Baltimore, Md., died suddenly of coronary thrombosis. He was only 55 years of age, and all of his friends and associates believed him to be in the prime of life. Dr. Wright was one of the early members to join the American College of Physicians from Baltimore; and while the greater part of his life was devoted to radiology, he never failed to attend all the local meetings and to keep his interest with the College.

Dr. Wright graduated from the University of Maryland School of Medicine in 1919. He was an Associate in Physiology from 1920–1923 and an Instructor in Medicine from 1923–1942 at his alma mater. For many years he was roentgenologist at South Baltimore General Hospital. He was a member of the Baltimore City Medical Society, Southern Medical Association, Radiological Society of North America, and had been a Fellow of the American College of Physicians since 1931. He was also a Diplomate of the American Board of Radiology.

Dr. Wright was one of my classmates and one that we, his fellow associates,

could always go to in time of need. He had great understanding of human nature; his loss will be a great one to his many friends in the medical profession.

WETHERBEE FORT, M.D., F.A.C.P.,
Governor for Maryland

DR. CHARLES SAUL DANZER

Dr. Charles Saul Danzer died on January 19, 1950, at his home, 38 East 63rd Street, New York City, at the age of 54. He was born in New York City, was graduated from the University and Bellevue Medical School in 1915, following which he did postgraduate work at Johns Hopkins University School of Medicine, Trudeau Sanatorium, and at the Universities of Vienna and Prague. For a time he was Assistant Professor of Experimental Medicine at New York Homeopathic Medical College, and an Attending Physician at Sea View Hospital. He subsequently served as an Instructor in Medicine at Columbia University College of Physicians and Surgeons, and for many years had been Attending Physician at Unity and Cumberland Hospitals, and at the Brooklyn Cancer Institute. He was also Director of Medicine at Shore Road Hospital, Brooklyn, and since 1934 had been Director of the Eastern Life Insurance Company of New York. He was a member of the New York Academy of Medicine, Society for Experimental Biology and Medicine, and the National Panel of the American Arbitration Association. Dr. Danzer had been a Fellow of the American College of Physicians since 1926. In addition to his heavy administrative duties as a Medical Director of a large life insurance company he found opportunity to devote much time to clinical medicine and made an enviable record.

ASA L. LINCOLN, M.D., F.A.C.P.,
Governor for Eastern New York

DR. JOHN AUGUSTUS TOOMEY

Medicine lost one of its unique pioneering personalities with the passing of John Augustus Toomey (F.A.C.P., 1926) on January 1, 1950, at the age of 60 years. Hypertensive, cardiovascular renal changes paved the way for the terminal cerebral hemorrhage.

Graduated from the Cleveland Law School in 1913 he practiced law in Ohio for one year. However, his basic interest in medical science prevailed, and he entered Western Reserve University School of Medicine in 1915, receiving his medical degree in 1919. Following his internship at Cleveland City Hospital, he took a residency in tuberculosis, becoming Medical Superintendent and Acting Director of this Cleveland institution. This prepared him to accept the Directorship of the new Department of Contagious Diseases at Cleveland City Hospital when it was organized in 1922, a position he continued to occupy until the time of his death. Dr. Toomey joined the faculty of his Alma Mater in 1920 as Demonstrator in Anatomy, advancing to the professorship of Clinical Pediatrics and Contagious Disease, a position he held at the time of his demise. Dr. Toomey served as interim Acting Director of the Department of Pediatrics at Western Reserve University during 1945.

Besides his teaching and clinical duties at the University, he cared for the children at the Parmadale Orphanage, St. Edward's Home and Merrick House Day Nursery.

During 1947–1948 Dr. Toomey was President of the American Academy of Pediatrics, and during the same period he served as President of the Western Reserve Medical Alumni Association. In June 1949 he was honored with the LL.D. degree by John Carroll University, his Alma Mater.

Dr. Toomey served as Chairman of the Committee on Therapeutic Procedures for Acute Infectious Diseases of the American Academy of Pediatrics, which edited from 1938 the annual edition of the "Red Book" guide to developments in the application of

immunization procedures and therapeutic practices for the control and treatment of contagious diseases. He published approximately 300 scientific papers and was a contributor to various systems of Pediatrics and Medicine on the subjects of his special field of interest.

John Toomey was a physician-teacher whose endeavors spanned both the clinical and research aspects of infectious diseases. He was an early and vigorous advocate of the concept that infantile paralysis may be contracted through the gastrointestinal tract. Early in 1922 he advocated immediate treatment in acute "polio," consisting of heat, massage, stimulation, exercise, and eventually a balanced gait—methods later popularized and widely adopted. In 1947 the National Foundation established one of its five National Centers for poliomyelitis for teaching and training at the Cleveland City Hospital, under Dr. Toomey's direction.

Many of his students and colleagues sought his counsel both professionally and personally, and his rare sympathy and understanding and friendliness and interest never failed to respond to their needs.

In 1918 he married Mary Louise Bagot of Anderson, Ind., whom he met while she was a dietitian at the Cleveland City Hospital. They had four children—Charles Hugh, a resident physician in Ophthalmology, Bellevue Hospital, New York City; Frances, now a senior student at Marquette University Medical School; Mrs. Mary Louise Quinn, a second year law student at Reserve; and John A., Jr., a student at Hobart College. What a legacy and what a heritage!

In 1942, addressing the graduating class of Western Reserve University Medical School, Dr. Toomey said: "No virtue is so noble as that of loyalty—loyalty towards our friends, our faith, our school, our country and our way of life." A loyal friend and true physician-teacher-investigator has left the scene of his loves and labors of three decades and more—the world having been left a better and healthier place in which to live because of his responsive loyalty to life's challenging opportunities.

CHARLES A. DOAN, F.A.C.P.,
Governor for Ohio

DR. DOUGLAS DAVISON BAUGH

Douglas Davison Baugh, B.S., M.D., F.A.C.P., Columbus, Miss., was born at Polkville, Miss., July 31, 1901. He graduated from the University of Mississippi, B.S., in 1927, from the University of Pennsylvania School of Medicine, M.D., 1929, and became a Fellow of the American College of Physicians in 1940. He did postgraduate work at Columbia University College of Physicians and Surgeons.

Dr. Baugh died on December 17, 1949, of coronary occlusion, age 48.

At one time Dr. Baugh was Assistant Superintendent of the State Charity Hospital at Jackson, Miss. For many years he was a member of the staff of Columbus Hospital and Doster Hospital and Clinic; Medical Consultant, Mississippi State College for Women; Associate Editor, "The Mississippi Doctor"; former Secretary, Chickasaw County Medical Society; member, Mississippi State Medical Association, Southern Medical Association and Fellow, American Medical Association; Director, The Baugh Clinic, founded by him in 1937; President, Lowndes County Medical Society.

Dr. Baugh achieved much as a physician and always carried with him the loyal and reciprocal friendship of his patients and colleagues. With easy bearing, with a humorous and kindly nature, and a penchant for telling humorous stories, Dr. Baugh was nevertheless a hard worker who wrought splendidly, thought deeply and logically, and spoke wisely and kindly. With his untimely and unexpected passing, the City of Columbus and the State of Mississippi lost an eminent and much loved physician. He is survived by his wife, the former Miss Mary Frances Jones, and three daughters.

JOHN G. ARCHER, M.D., F.A.C.P.,
Governor for Mississippi

DR. A. L. BENEDICT

Dr. A. L. Benedict, A.B., A.M., M.D., F.A.C.P., was born in 1865, graduated from the University of Michigan, A.B., 1887, from the University of Buffalo School of Medicine, M.D., 1888, and from the University of Pennsylvania School of Medicine, M.D., 1889. He received his A.M. degree from Ohio Wesleyan University in 1891. He did some postgraduate work at Hotel Dieu, Paris, France. During World War I he served in the Medical Corps of the U. S. Army with the rank of Captain, later serving as Major in the New York National Guard.

Dr. Benedict was the author of three books, "Practical Dietetics" (G. P. Englehard & Co., Chicago, 1904), "Golden Rules of Dietetics" (C. V. Mosby Co., St. Louis, 1908) and "Why We Are Men and Women" (Allen Ross & Co., N. Y., 1929). He was also the author of numerous articles and essays, and for two was awarded first prize in the contest conducted by the Medical Society of the State of New York in connection with the Merritt H. Cash Prize Essay. An article by him entitled "Gastric Proteolysis," published in the Journal of the American Medical Association in 1901, was awarded the gold medal of the Association. Dr. Benedict's major interest was gastroenterology.

He was a member of the Erie County Medical Society, the Medical Society of the State of New York, the Buffalo Academy of Medicine, serving the latter organization as Secretary from 1892–1894. Additionally, he was a member of the Buffalo Society of Natural Science, the Buffalo Historical Society, the Delta Epsilon and Nu Sigma Nu Fraternities. Dr. Benedict was a charter Fellow of the American College of Physicians, having been inducted in 1916. Few, indeed, remain from the original ranks of membership.

Dr. Benedict practiced medicine in Buffalo for 55 years. He died from a heart attack on January 14, 1950, at the age of 85, while making a professional call in Buffalo. He was highly respected by his colleagues. The medical profession and the citizens of Buffalo have sustained an irreparable loss in his death.

EDWARD C. REIFENSTEIN, M.D., F.A.C.P.,
Governor for Western New York

DR. EDWARD CHARLES KOENIG

Born in Tonawanda, N. Y., 1877. Graduate of the University of Buffalo School of Medicine, 1904. Formerly Assistant Professor of Roentgenology, University of Buffalo School of Medicine. He served overseas during World War I. He was formerly Consulting Radiologist of the Children's Hospital and was in charge of the X-Ray Department, Buffalo General Hospital, where he died December 19, 1949, of acute coronary occlusion. Dr. Koenig was a Diplomate of the American Board of Radiology and a Fellow of the American Medical Association. He was a member of the American Roentgen Ray Society; a member of the Radiological Society of North America; and a member of the American College of Radiology. He was a Fellow of the American College of Physicians since April 3, 1922, and a Life Member since February 25, 1947.

Dr. Koenig was a very understanding physician. To him the relationship to the patient was very important. He will be greatly missed by the many grateful patients in the Buffalo area. He was extremely helpful and generous with the younger men in the profession and was ever willing to extend a helping hand. Dr. Koenig's passing leaves a vacancy in the community and in the profession which will be difficult to fill.

Dr. Koenig is survived by his wife, Ruby H., and one son, Edward C. Koenig, Jr.

EDWARD C. REIFENSTEIN, M.D., F.A.C.P.,
Governor for Western New York

DR. ARTHUR PARKER HITCHENS

Arthur Parker Hitchens, M.D., F.A.C.P., was born in Delmar, Del., September 14, 1877. He died at Philadelphia on December 10, 1949. Dr. Hitchens graduated from the former Medico-Chirurgical College, Philadelphia, in 1898, and for twelve years thereafter was Bacteriologist at the Mulford Biological Laboratories, resigning to enter the Army Medical Corps in 1918. He joined the U. S. Public Health Service in 1920, and organized the School of Public Health and Preventive Medicine of the University of the Philippines. In 1939, he was appointed George S. Pepper Professor of Public Health and Preventive Medicine at the University of Pennsylvania. He was widely known as a Public Health expert and until recently was the Director of the Bureau of Laboratories of the Pennsylvania State Board of Health. He at one time served as Editor-Trustee of the "Bergey Manual of Determinative Bacteriology," as Editor of "Biological Abstracts," and was formerly a member of the Executive Council of the Union of American Biological Societies. In 1941, he was President of the Pennsylvania Public Health Association. He served as Commissioner of Health from 1944 to 1948 in the City of Wilmington, Del. He became a Fellow of the American College of Physicians in 1936, and thereafter always exhibited an active and abiding interest in the College.

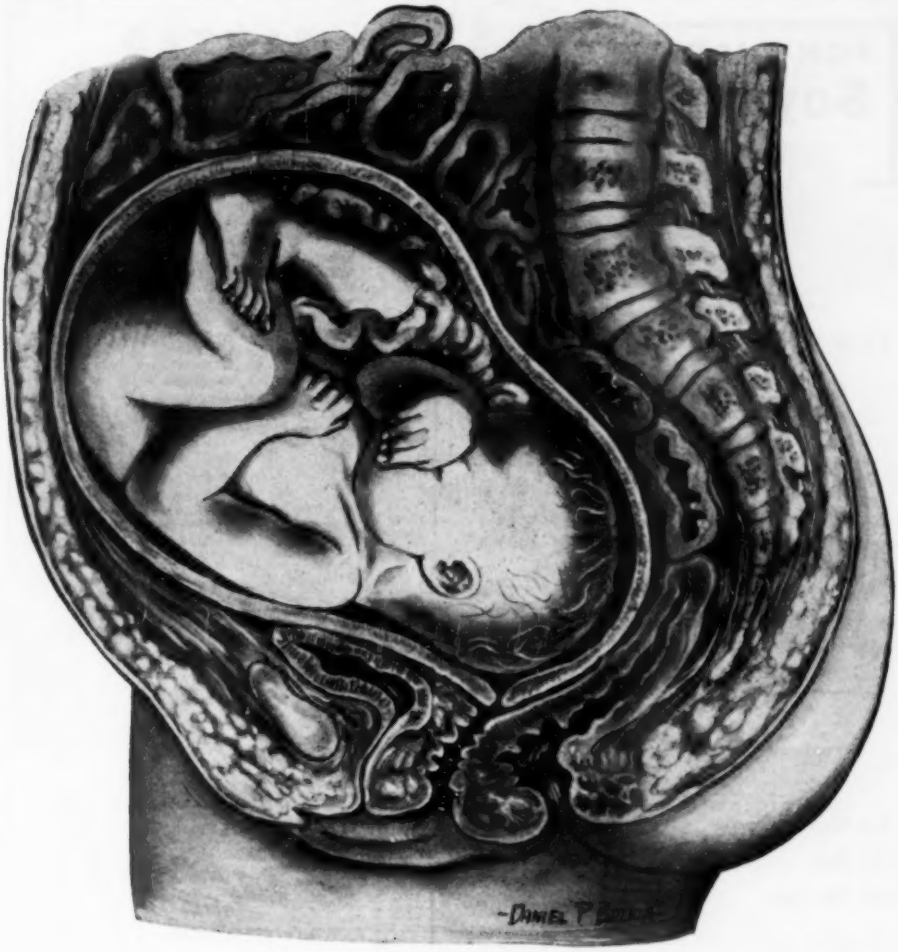
DR. GEORGE BURGESS FOSTER, JR.

George Burgess Foster, Jr., M.D., D.P.H., F.A.C.P., was born in Salem, Mass., July 27, 1884, and died December 31, 1949, of coronary thrombosis.

Dr. Foster was considered one of the leading laboratory experts of the Medical Corps of the Army, and during the early part of his service was quite active in the operation of bacteriological and clinical laboratories in the various Army hospitals. He did some of the earlier filtration experiments on the secretions of individuals with acute respiratory infection and transferred this material to human volunteers. During the first World War he had charge of the large Army laboratory in Dijon, where he did a top-notch job. During the second World War he was Commanding Officer of the O'Reilly General Hospital in Springfield, Mo., which was generally considered as one of the best operated hospitals in the Zone of the Interior.

Throughout his life General Foster had a keen interest in scientific medicine and in its application to preventive medicine and public health. Dr. Foster graduated from Wesleyan Academy in 1903, and from Jefferson Medical College of Philadelphia in 1907. He was an Honor Graduate of Army Medical School in 1910, and received his Doctor of Public Health degree from Harvard Medical School in 1916. He entered the Medical Corps of the U. S. Army on June 20, 1910, as First Lieutenant and served during World Wars I and II. He was awarded the Legion of Merit from this country and the Legion of Honor from France. Formerly he was Commanding Officer of the Tripler General Hospital, Honolulu, T. H. He was awarded a Bronze Plaque by the Springfield, Mo., Chamber of Commerce as "Man of the Year" in 1945 for his activities in coördinating the welfare of the hospital and that of the community. He retired from the Army, August 31, 1946, with the rank of Brigadier General. Since 1946, he was Medical Director of the Cambridge (Mass.) City Hospital. He was a Fellow of the American Medical Association and a member of the American Hospital Association, Massachusetts Hospital Association, the New England Hospital Assembly, the Massachusetts Medical Society, American Public Health Association and the Harvard Club of Boston. He had been a Fellow of the American College of Physicians since 1935.

CHESTER S. KEEFER, M.D., F.A.C.P.,
Governor for Massachusetts



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*Evans, James A., Bartels, Carl C., *Results of High Dorsolumbar Sympathectomy for Hypertension,* Annals of Internal Medicine 30: 307-329 (February) 1949.

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ANNALS OF INTERNAL MEDICINE

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